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PCT/SE99/02478

PA NT COOPERATION TREAT

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

Date of mailing (day/month/year) 11 September 2000 (11.09.00)	
Applicant's or agent's file reference J 2090-1 WO	**IMPORTANT NOTIFICATION**
International application No. PCT/SE99/02478	**International filing date** (day/month/year) 23 December 1999 (23.12.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
LOCH, James, III Astra Arcus USA, Inc. P.O. Box 20890 Rochester, NY 14603 United States of America	US	US
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	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

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LOCH, James, III AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, MA 02451 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

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[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

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Intellectual Property, Patents
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International application No. PCT/SE99/02478	**International filing date** (day/month/year) 23 December 1999 (23.12.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
MULLEN, George AstraZeneca R&D Boston 35 Gatehouse Drive Waltham, MA 02451 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

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PATENT COOPERATION TREATY

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To:

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

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1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

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State of Residence: US
Telephone No.:
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(PCT Rule 61.2)

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International application No. PCT/SE99/02478	**Applicant's or agent's file reference** J 2090-1 WO
International filing date (day/month/year) 23 December 1999 (23.12.99)	**Priority date** (day/month/year) 15 January 1999 (15.01.99)
Applicant LOCH, James, III et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:
19 July 2000 (19.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

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[ ] was not

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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

SE9902478

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(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

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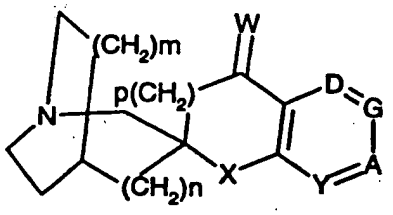
(54) Title: NOVEL SPIROAZABICYCLIC HETEROCYCLIC COMPOUNDS

(57) Abstract

A compound of formula (I) wherein n is 0 or 1; m is 0 or 1; p is 0 or 1; X is oxygen or sulfur; Y is CH, N or NO; W is oxygen, H_2 or F_2; A is N or $C(R^2)$; G is N or $C(R^3)$; D is N or $C(R^4)$; with the proviso that no more than one of A, G, and D is nitrogen, but at least one of Y, A, G, and D is nitrogen or NO; R^1 is hydrogen or C_1 to C_4 alkyl; R^2, R^3, and R^4 are independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $–OSO_2CF_3$ or R^2 and R^3, or R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substituents: independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $–OSO_2CF_3$; R^5 and R^6 are independently hydrogen, C_1–C_4 alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond; j is 2 to 7, k is 0 to 2; R^7, R^8, R^9, R^{10}, and R^{11} are independently C_1–C_4 alkyl, aryl, or heteroaryl, or an enantiomer thereof, and the pharmaceutically acceptable salts thereof, processes for preparing them, composition containing them, and their use in therapy, especially in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders.



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Novel spiroazabicyclic heterocyclic compounds.

TECHNICAL FIELD

This invention relates to novel spiroazabicyclic heterocyclic amines or pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy. A further object is to provide active compounds which are potent ligands for nicotinic acetylcholine receptors (nAChR's).

BACKGROUND OF THE INVENTION

The use of compounds which bind nicotinic acetylcholine receptors in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease has been discussed in McDonald et al. (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; and in Williams et al. (1994) "Neuronal Nicotinic Acetylcholine Receptors," Drug News & Perspectives, vol. 7, pp. 205-223.

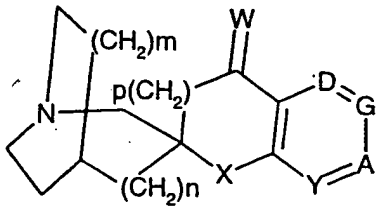
US Patent 5,468,875 discloses N-alkylcarbamic acid 1-azabicyclo[2.2.1]hept-3-yl esters which are centrally active muscarinic agents useful in the treatment of Alzheimer's disease and other disorders.

N-(2-alkoxyphenyl)carbamic acid 1-azabicyclo[2.2.2]octan-3-yl esters are disclosed in Pharmazie, vol. 48, 465-466 (1993) along with their local anesthetic activity. N-phenylcarbamic acid 1-azabicyclo[2.2.2]octan-3-yl esters substituted at the *ortho* position on the phenyl ring are described as local anaesthetics in *Acta Pharm. Suecica*, 7, 239-246 (1970).

Furopyridines useful in controlling synaptic transmission are disclosed in WO 97/05139.

DISCLOSURE OF THE INVENTION

According to the invention it has been found that a compound of formula I



I

wherein n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

Y is CH, N or NO

X is oxygen or sulfur;

W is oxygen, H_2 or F_2;

A is N or C(R^2) ;

G is N or C(R^3) ;

D is N or C(R^4) ;

with the proviso that no more than one of A, G, and D is nitrogen but at least one of Y, A, G, and D is nitrogen or NO;

R^1 is hydrogen or C_1–C_4 alkyl;

R^2, R^3, and R^4 are independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $–OSO_2CF_3$, or R^2 and R^3, or R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively containing between zero and two nitrogen atoms, and substituted with one to two of the following substituents: independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–

C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, OSO_2CF_3 ;

R^5 and R^6 are independently hydrogen, C_1–C_4 alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond;

j is 2 to 7;

k is 0 to 2;

R^7, R^8, R^9, R^{10}, and R^{11} are independently C_1–C_4 alkyl, aryl, or heteroaryl,

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof is a potent ligand for nicotinic acetylcholine receptors.

Unless otherwise indicated, the C_1–C_4 alkyl groups referred to herein, e.g., methyl, ethyl, n-propyl, n-butyl, i-propyl, i-butyl, t-butyl, s-butyl, may be straight-chained or branched, and the C_3–C_4 alkyl groups may also be cyclic, e.g., cyclopropyl,cyclobutyl.

Unless otherwise indicated, the C_1–C_6 alkyl groups referred to herein, e.g., methyl, ethyl, n-propyl, n-butyl, i-propyl, i-butyl, t-butyl, s-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl, or i-hexyl may be straight-chained or branched, and the C_3–C_6 alkyl groups may also be cyclic, e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Unless otherwise indicated, the C_1–C_4 alkoxy groups referred to herein, e.g., methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, s-butoxy, may be straight-chained or branched.

Unless otherwise indicated, the C_2–C_4 alkenyl groups referred to herein may contain one or two double bonds, e.g., ethenyl, i-propenyl, n-butenyl, i-butenyl, allyl, 1,3-butadienyl.

Unless otherwise indicated, the C_2–C_4 alkynyl groups referred to herein contain one triple bond, e.g., ethynyl, propynyl, 1- or 2-butynyl.

Halogen referred to herein may be fluoride, chloride, bromide, or iodide.

Unless otherwise indicated, aryl refers to a phenyl ring optionally substituted with one to three of the following substituents: hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$;

Unless otherwise indicated, heteroaryl refers to a five- or six-membered aromatic ring containing one or two nitrogen atoms, such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, imidazolyl or pyrazolyl, with the carbon atoms of that ring optionally substituted with one to three of the following substituents: hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$; R^5 and R^6 may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond, and where j is 2 to 7, preferably 2 to 3, and k is 0 to 2, so as to form a 3–7 membered ring, preferably a 5- or 6-membered ring, for example pyrrolidinyl, imidazolidinyl piperazinyl, piperidyl, morpholinyl, or thiomorpholinyl.

R^2 and R^3 may together form another six membered aromatic or heteroaromatic ring sharing A and G containing between zero and two nitrogen atoms refers to groups such as quinoline, 1,5-, 1,6-, 1,7-, or 1,8-diazanaphthalene.

R^3 and R^4 may together form another six membered aromatic or heteroaromatic ring sharing G and D containing between zero and two nitrogen atoms refers to groups such as isoquinoline, 2,5-, 2,6-, 2,7-, or 2,8-diazanaphthalene.

Preferred compounds of the invention are compounds of formula I wherein m is 1; n is 0; p is 0; X is oxygen; W is H_2; A is $C(R^2)$; G is $C(R^3)$; D is $C(R^4)$.

Preferred compounds of the invention include the following:

- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)- furo[2,3-b]pyridine];
- 1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline];

- 5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline];
- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline];
- 5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(1-azetidinyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carbonitrile];
- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carboxamide];
- 5'-N'-(3-chlorophenyl)aminocarbonylminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N'-(2-nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 4'-phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 4'-(4-N-methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 4'-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine];
- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine];
- spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide];
- spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile];
- 6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];
- 6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];

and the enantiomers, and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of the invention are compounds of formula I wherein m is 1; n is 0; p is 0; X = oxygen; W is H_2; A = CH, D = CH, and G = C(R3), including the following compounds:

- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide];
- 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

- 5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
  5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(1-azetidinyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- 5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine];
- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine-5'carbonitrile];

- spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)furo[2,3-b]pyridine-5'carboxamide];
- 5'-N'-(3-chlorophenylaminocarbonylminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
- 5'-N'-(2-nitrophenylaminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

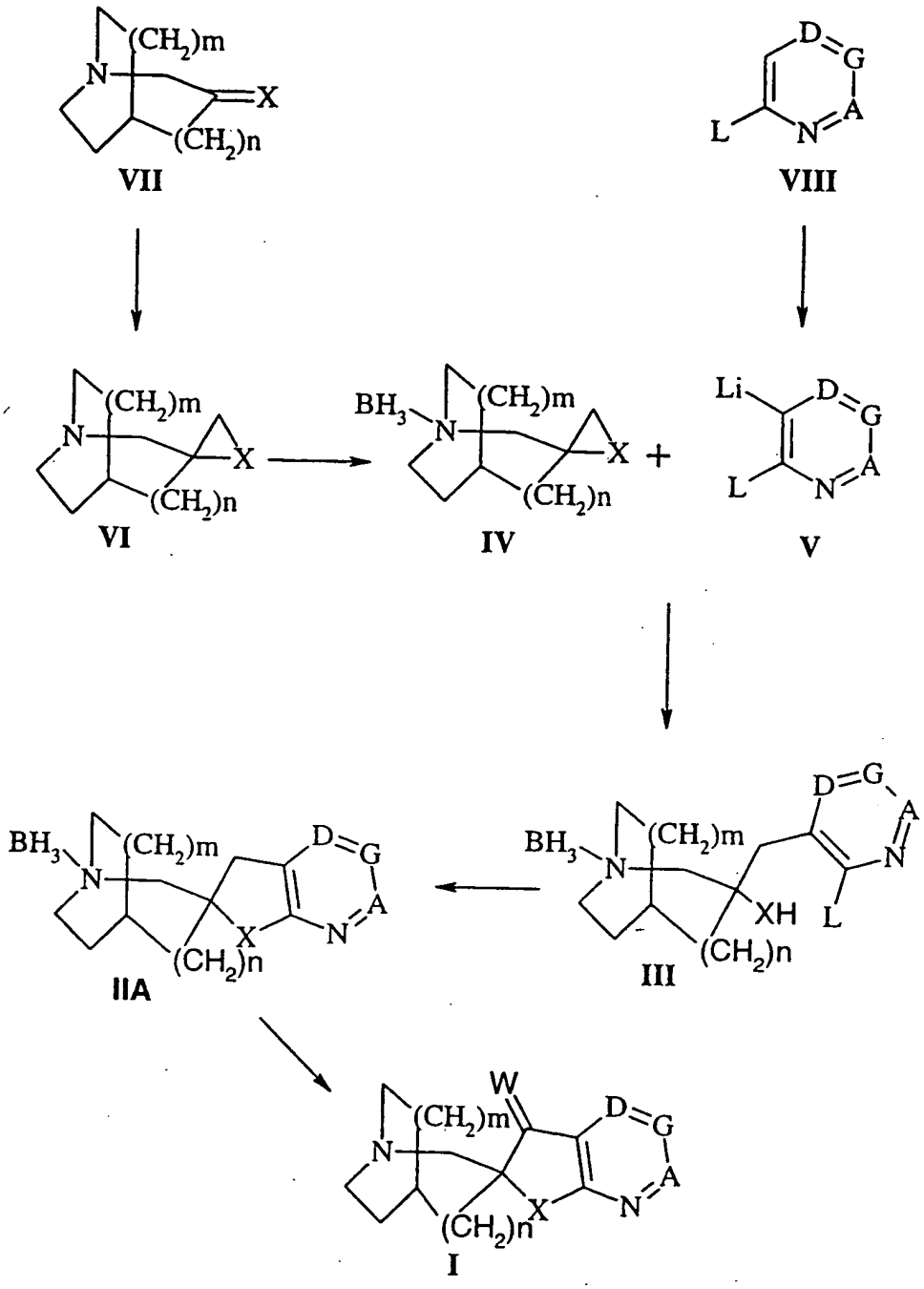
Methods of Preparation

In the reaction schemes and text that follow, A, G, D, X, W, Y, Z, m, n, and p, unless otherwise indicated, are as defined above for formula I.

(A) Compounds wherein p is 0 and Y is N

The compounds of formula I, wherein p is 0 and Y is N, may be prepared according to the methods outlined in Scheme I.

Scheme I (p = 0)



Compounds of formula I where W=H_2 and p is 0 may be prepared from the deprotection of a compound of formula IIA using acid in a suitable solvent. Suitable acids include mineral, organic and Lewis acids, for example, hydrochloric and hydrobromic acid, sulfuric acid, triflic acid, methanesulfonic acid, and boron trifluoride etherate. The preferred acid is hydrobromic acid. Suitable solvents include acetone, butanone, ethanone, and pinacolone. The preferred solvent is acetone. The reaction is usually conducted at a temperature from about –10°C to about 100°C, preferably about 0°C to about 60°C. Alternatively the deprotection may be conducted by heating the borane complex in alcoholic solvents. A preferred method is by refluxing a ethanolic solution of the complex.

Compounds of formula I where W=O (oxygen) and p is 0 may be prepared by the oxidation of compounds of formula IIA, for example using selenium dioxide, or by reaction first with N-bromosuccinimide then with sodium bicarbonate and methylsulfoxide, followed by removal of the borane group as described above.

Compounds of formula I where W=F_2 and p is 0 may be prepared from compounds of formula I where W=O by reaction with a fluorinating agent, for example diethylaminosulfur trifluoride.

Compounds of formula IIA may be prepared from the cyclization of a compound of formula III wherein L is fluoro, chloro, bromo, iodo, –OCH_3, –SPh, –SCH_3, –SO_2Ph, or –SO_2CH_3 in the presence of a base in an inert solvent. Suitable bases include sodium hydride, sodium amide, potassium hydride, potassium *t*-amylate, potassium *t*-butoxide, and potassium bis(trimethylsilyl)amide. The preferred base is sodium hydride. Suitable inert solvents include N,N-dimethylformamide, N-methylpyrrolidin-2-one, ethers such as diethyl ether, tetrahydrofuran, and 1,4-dioxane, and dimethylsulfoxide. The preferred inert solvent is N,N-dimethylformamide. The reaction is usually conducted at a temperature from about10°C to about 100°C, preferably about 20°C to about 66°C.

Compounds of formula III wherein L is fluoro, chloro, bromo, iodo, –OCH_3, –SPh, –SCH_3,

$-SO_2Ph$, or $-SO_2CH_3$ may be prepared by the reaction of a compound of formula IV with a compound of formula V wherein L is defined as above in an inert solvent. Suitable inert solvents include diethyl ether, tetrahydrofuran and 1,4-dioxane. The preferred inert solvent is tetrahydrofuran. The reaction is usually conducted at a temperature from about –100°C to about 0°C, preferably about –78°C to about –25°C.

Compounds of formula V wherein L is defined as above may be prepared from a compound of formula VIII wherein L is defined as above using a lithium base and a proton transfer agent in an inert solvent. Suitable lithium bases include lithium diisopropylamide, *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. The preferred lithium base is phenyllithium. Suitable proton transfer agents include hindered secondary amines such as diisopropylamine and 2,2,6,6-tetramethylpiperidine. The preferred proton transfer agent is diisopropylamine. Suitable inert solvents include diethyl ether, tetrahydrofuran and 1,4-dioxane. The preferred inert solvent is tetrahydrofuran. The reaction is usually conducted at a temperature from about –100°C to about 0°C, preferably about –78°C to about –25°C. Compounds of formula V are usually taken directly into the reaction with compounds of formula IV without purification.

Compounds of formula IV may be prepared from the reaction of a compound of formula VI with borane (BH_3 or B_2H_6) in an inert solvent. Borane in tetrahydrofuran is preferred. Suitable inert solvents include diethyl ether, tetrahydrofuran and 1,4-dioxane. The preferred inert solvent is tetrahydrofuran. The reaction is usually conducted at a temperature from about –10°C to about 66°C, preferably about 0°C to about 20°C.

Compounds of formula VIII are known, e.g., either commercially available or may be prepared by methods known to one skilled in the art (see e.g, The Chemistry of Heterocyclic Compounds, Pyridine and Its Derivatives, Part 1, E. Klingsberg, Ed., Interscience Publishers, Inc, NY, 1960).

Compounds of formula VI may be prepared from compounds of formula VII by methods known to one skilled in the art. For example, compounds of formula VI wherein X

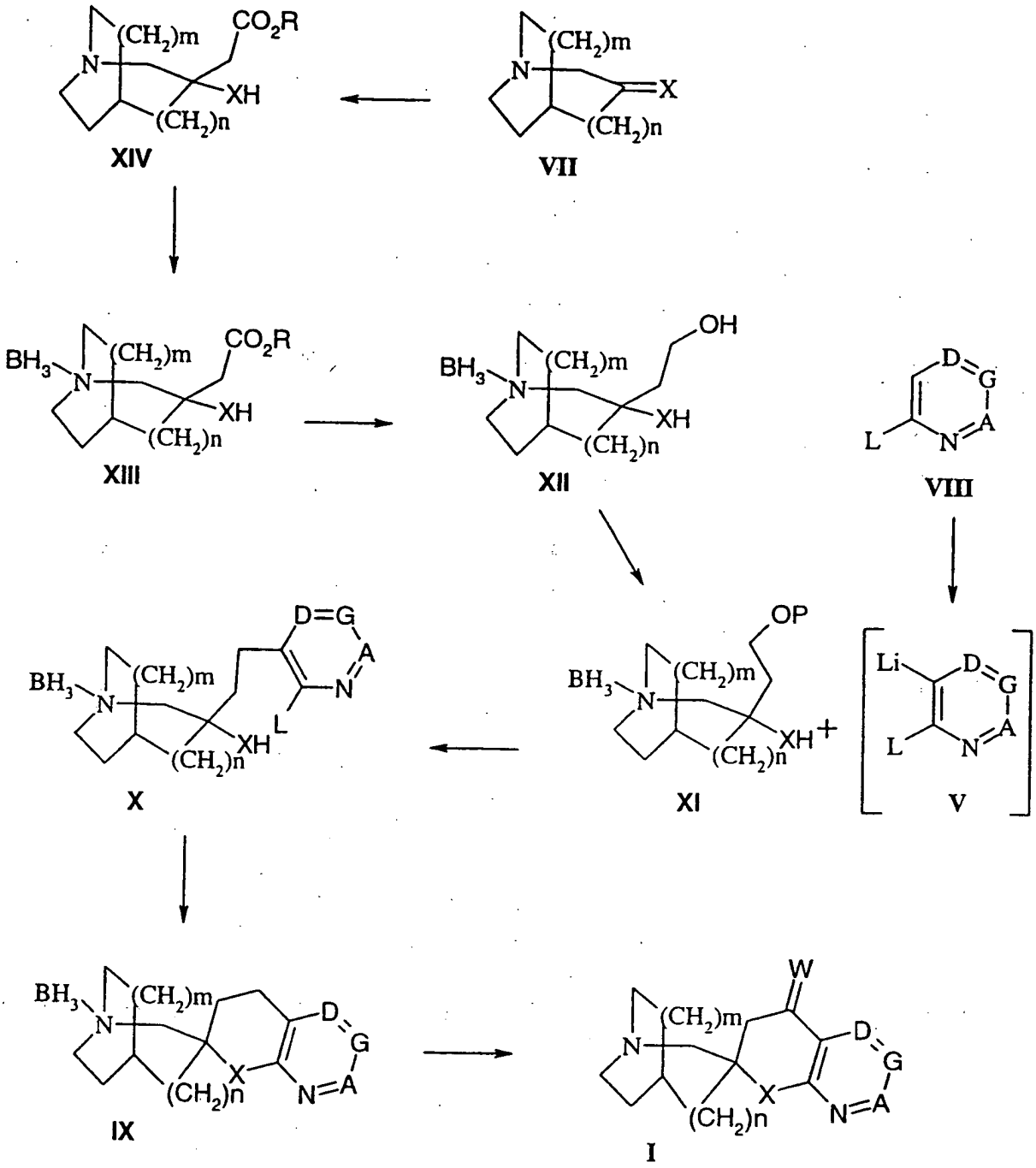
represents oxygen may be prepared from the corresponding compound of formula VII wherein X represents the oxygen of a ketone using one of the reagents well known in the art for preparation of oxiranes from ketones (see e.g. the reactions referenced in J. March, "Advanced Organic Chemistry" (1985) 3rd Edition, page 1161). Compounds of formula VI wherein X represents sulfur may be prepared from the corresponding compound of formula VII wherein X represents either oxygen or sulfur using one of the methods well known in the art for preparation of episulfides from ketones or thioketones (see, e.g. the reactions referenced in J. March, "Advanced Organic Chemistry" (1985) 3rd Edition, pages 866-867).

Compounds of formula VII are known, e.g., either commercially available or may be prepared by methods known to one skilled in the art (see, e.g, The Chemistry of Heterocyclic Compounds, Heterocyclic Systems with Bridgehead Nitrogen Atoms, Part 2, W.L. Mosby, Ed., Interscience Publishers, Inc, NY, 1961).

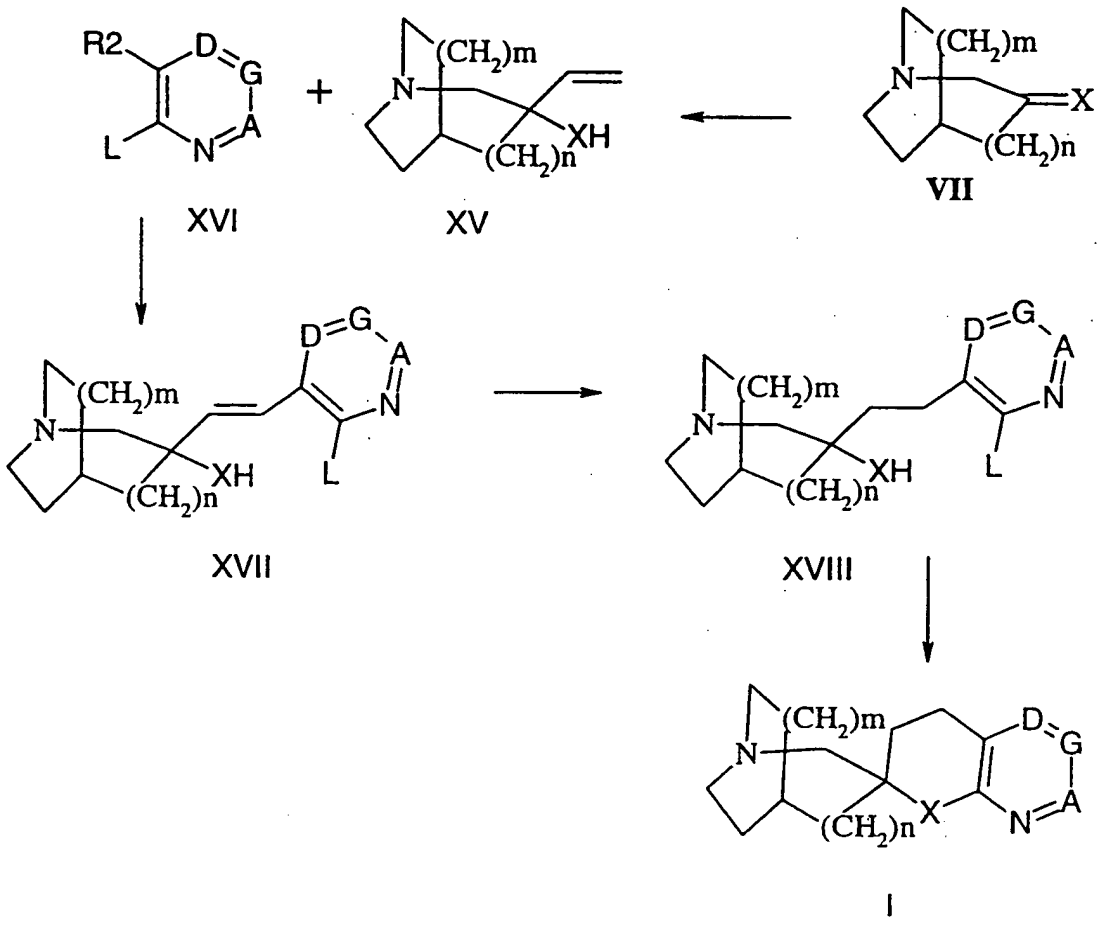
(B) Compounds wherein p is 1 and Y is N

The compounds of formula I (p = 1) may be prepared according to the methods described in Scheme II or Scheme III, below.

Scheme II (p = 1)



Scheme III



Compounds of formula I where W is H_2 and p is 1 may be prepared from the deprotection of a compound of formula IX using acid in a suitable solvent. Suitable acids include mineral, organic and Lewis acids, for example, hydrochloric and hydrobromic acid, sulfuric acid, triflic acid, methanesulfonic acid and borontrifluoride etherate. The preferred acid is hydrobromic acid. Suitable solvents include acetone, butanone, ethanone, and pinacolone. The preferred solvent is acetone. The reaction is usually conducted at a temperature from about –10°C to about 100°C, preferably about 0°C to about 60°C. Alternatively the deprotection may be conducted by heating the borane complex in alcoholic solvents. A preferred method is by refluxing a ethanolic solution of the complex.

Compounds of formula I where W=O and p is 1 may be prepared by the oxidation of compounds of formula I, where W is H_2 and p is 1, using selenium dioxide, or by reaction first with N-bromosuccinimide then with sodium bicarbonate and methylsulfoxide, followed by removal of the borane group as described above.

Compounds of formula I, where W = F_2 and p is 1, may be prepared from compounds of formula I, where W=O and p is 1, by reaction with diethylaminosulfur trifluoride.

Compounds of formula IX may be prepared from the cyclization of a compound of formula X wherein L is fluoro, chloro, bromo, iodo, $-OCH_3$, –SPh, $-SCH_3$, $-SO_2Ph$, or $-SO_2CH_3$ in the presence of a base in an inert solvent. Suitable bases include sodium hydride, sodium amide, potassium hydride, potassium t-amylate, potassium t-butoxide, and potassium bis(trimethylsilyl)amide. The preferred base is sodium hydride. Suitable inert solvents include N,N-dimethylformamide, N-methylpyrrolidin-2-one, ethers such as diethyl ether, tetrahydrofuran, and 1,4-dioxane, and dimethylsulfoxide. The preferred inert solvent is N,N-dimethylformamide. The reaction is usually conducted at a temperature from about –10°C to about 100°C, preferably about 20°C to about 66°C.

Compounds of formula X wherein L is fluoro, chloro, bromo, iodo, $-OCH_3$, –SPh, $-SCH_3$, $-SO_2CH_3$ may be prepared by the reaction of a compound of formula XI with a compound of formula V wherein L is defined as above in an inert solvent. Suitable inert solvents

include diethyl ether, tetrahydrofuran and 1,4-dioxane. The preferred inert solvent is tetrahydrofuran. The reaction is usually conducted at a temperature from about –100°C to about 0°C, preferably about –78°C to about –25°C.

Compounds XI, wherein P is $-SO_2Ph$, $-SO_2PhCH_3$-4, $-SO_2CH_3$ or $-SO_2CF_3$ may be prepared from compounds XII by reaction with a reagent such as toluenesulfonyl chloride, methanesulfonyl chloride, or trifluoromethanesulfonyl chloride in the presence of an amine base such as triethylamine, dimethylaminopyridine, or diazabicyclo[4.3.0]nonane in an inert solvent. Suitable inert solvents may be dichloromethane, chloroform, tetrahydrofuran, diethyl ether, or dioxane. The preferred inert solvent is dichloromethane. The reaction is usually conducted at a temperature from about –10°C to about 66°C, preferably about 0°C to about 20°C.

Compounds XII may be prepared from compounds of formula XIII by reduction with reagents such as lithium aluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride, sodium or lithium triethylboride, lithium tri-sec-butylborohydride, potassium tri-sec-butylborohydride, sodium tri-sec-butylborohydride or lithium borohydride. The preferred reagent is lithium borohydride. Suitable inert solvents include diethyl ether, tetrahydrofuran and 1,4-dioxane. The preferred inert solvent is tetrahydrofuran. The reaction is usually conducted at a temperature from about –78°C to about 66°C, preferably about –10°C to about 20°C.

Compounds of formula XIII, wherein R is C_1–C_6 alkyl, $-CH_2$-Ar, or Ar, where Ar is phenyl optionally substituted with one to three of the following substitutents: halogen , C_1–C_4 alkyl, or C_1–C_4 alkoxy, may be prepared from the reaction of a compound of formula XIV with borane (BH_3 or B_2H_6) in an inert solvent. Borane in tetrahydrofuran is preferred. Suitable inert solvents include diethyl ether, tetrahydrofuran and 1,4-dioxane. The preferred inert solvent is tetrahydrofuran. The reaction is usually conducted at a temperature from about –10°C to about 66°C, preferably about 0°C to about 20°C.

Compounds of formula XIV are known, e.g., either commercially available or may be prepared from compounds of formula VII by methods known to one skilled in the art for the preparation of β-hydroxy esters from the reaction of esters and ketones (see, e.g. the reactions referenced in J. March, "Advanced Organic Chemistry" (1985) 3rd Edition, page 439).

Compounds of formula I where W is H_2 and p is 1 may be prepared from the cyclization of a compound of formula XVIII wherein L is fluoro, chloro, bromo, iodo, $-OCH_3$, $-SPh$, $-SCH_3$, $-SO_2Ph$, or $-SO_2CH_3$ in the presence of a base in an inert solvent. Suitable bases include sodium hydride, sodium amide, potassium hydride, potassium t-amylate, potassium t-butoxide, and potassium bis(trimethylsilyl)amide. The preferred base is sodium hydride. Suitable inert solvents include N,N-dimethylformamide, N-methylpyrrolidin-2-one, ethers such as diethyl ether, tetrahydrofuran, and 1,4-dioxane, and dimethylsulfoxide. The preferred inert solvent is N,N-dimethylformamide. The reaction is usually conducted at a temperature from about –10°C to about 100°C, preferably about 20°C to about 66°C.

Compounds of formula XVIII wherein L is defined as above may be prepared by catalytic hydrogenation of a compound of formula XVII using catalysts such as palladium on carbon, palladium hydroxide on carbon, palladium oxide, platinum on carbon, platinum oxide, Raney nickel, or rhenium on carbon in an inert solvent. Suitable inert solvents include methanol, ethanol, aqueous methanol or ethanol and ethyl acetate. The preferred solvent is ethanol. The reaction is usually conducted at a temperature from about 0°C to about 100°C, preferably about 20°C to about 50°C.

Compounds of formula XVII wherein L is defined as above may be prepared by reaction of a compound of formula XV with a compound of formula XVI using a palladium catalyst, together with a suitable ligand, base, and solvent. Suitable palladium catalysts include palladium acetate. Suitable ligands include phosphine ligands, such as triphenylphosphine or tri-o-tolylphosphine. Suitable bases include amines and inorganic bases, such as triethylamine, diisopropylethylamine, sodium carbonate or tetrabutylammonium acetate. Suitable solvents include dimethylformamide or acetonitrile.The reaction is usually

conducted at a temperature from about 0°C to about 140°C, preferably about 20°C to about 85°C.

Compounds of formula XVI, where L is defined as above and R^2 is chloro, bromo, iodo, fluoro, trifluoromethylsulfonyl, toluenesulfonyl or methylsulfonyl may be prepared by literature methods from commercially available materials.

Compounds of formula XV may be prepared from compounds of formula VII by methods known to one skilled in the art for the preparation of allyl alcohols from ketones using vinylmetal salts such as vinylmagnesium bromide.

(C) Compounds wherein p is 0 or 1

Compounds of formula I wherein R^2, R^3, or R^4 is halogen may be prepared from compounds of formula I wherein the corresponding substituent is hydrogen by reaction with a suitable halogenating agent, for example bromine in acetic acid. The transformation may require the addition of an acidic catalyst, such as the corresponding iron trihalide.

Compounds of formula I wherein R^2, R^3, or R^4 is C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl may be prepared from compounds of formula I wherein the corresponding substituent is halogen or OSO_2CF_3 by reaction with an appropriate alkyl, alkenyl, alkynyl, aryl or heteroaryl stannane reagent, in the presence of a suitable organometallic catalyst, for example tetrakis(triphenylphosphine)palladium (0), in a suitable solvent, for example 1,2-dimethoxyethane.

Compounds of formula I wherein R^2, R^3, or R^4 is aryl, heteroaryl may be prepared from compounds of formula I wherein the corresponding substituent is halogen or OSO_2CF_3 by reaction with an aryl or heteroaryl boronic acid, in the presence of a suitable organometallic catalyst, for example tetrakis(triphenylphosphine)palladium (0), in a suitable solvent, for example 1,2-dimethoxyethane.

Compounds of formula I wherein R^2, R^3, or R^4 is NO_2 may be prepared from compounds of formula I wherein the corresponding substituent is hydrogen by nitration using a suitable nitrating agent, for example nitric acid in concentrated sulfuric acid.

Compounds of formula I wherein R^2, R^3, or R^4 is NH_2 may be prepared from compounds of formula I wherein the corresponding substituent is NO_2 by reduction using a suitable procedure, for example hydrogenation. Hydrogenation may be performed by the reaction of a compound, dissolved in a suitable solvent, with gaseous hydrogen in the presence of a suitable catalyst. Suitable solvents include methanol, ethanol, and acetic acid. Suitable catalysts include palladium, for example as 10% palladium on carbon.

Compounds of formula I wherein R^2, R^3, or R^4 is NR^5R^6 wherein R^6 is alkyl may be prepared from compounds of formula I wherein the corresponding substituent is NHR^5 by a suitable alkylation procedure. Also, compounds of formula I wherein R^2, R^3, or R^4 is NR^5R^6 wherein R^5 and R^6 are identical alkyl groups or R^5 and R^6 together are $(CH_2)_jQ(CH_2)_k$ may be prepared from compounds of formula I wherein the corresponding substituent is NH_2 by a suitable alkylation procedure. Suitable alkylation procedures may include treatment with a suitable alkyl halide or sulfonate ester and base, for example sodium hydride, in a suitable solvent, for example DMF, or treatment with a suitable aldehyde or ketone in the presence of an acidic catalyst, for example zinc chloride, a reducing agent, for example sodium cyanoborohydride, and solvent, for example ethanol.

Compounds of formula I wherein R^2, R^3, or R^4 is OSO_2CF_3 may be prepared from compounds of formula I wherein the corresponding substituent is OH by reaction with trifluoromethanesulfonic anhydride in the presence of a suitable base, for example 2,6-di-t-butylpyridine, in a suitable solvent, for example dichloromethane.

Compounds of formula I wherein R^2, R^3, or R^4 is NR^5R^6 may also be prepared from compounds of formula I wherein the corresponding substituent is halide or OSO_2CF_3 by substitution with the appropriate amine NHR^5R^6. Suitable procedures include nucleophilic displacement, involving treatment with the amine, in excess or in the presence of an added

base, and a suitable solvent, for example DMSO, or organometallic complex catalysed substitution, involving treatment with the amine in the presence of a suitable organometallic complex, for example complexes of palladium with chelating phosphine ligands, as described in J. Org. Chem., 1996, vol. 61, pp. 7240.

Compounds of formula I wherein R^2, R^3, or R^4 is $NR^5C(O)R^7$ may be prepared from compounds of formula I wherein the corresponding substituent is NH_2 by a suitable acylation procedure. Suitable acylation procedures include treatment with a carboxylic acid chloride $R^6C(O)Cl$ in the presence of an optional nucleophilic catalyst, such as 4-(N,N-dimethylamino)pyridine, a base, for example pyridine or triethylamine, and a suitable solvent, for example tetrahydrofuran, or, alternatively, treatment with a carboxylic acid $R_6C(O)OH$ with a coupling agent, for example 1,3-dicyclohexylcarbodiimide, in a suitable solvent, for example tetrahydrofuran.

Compounds of formula I wherein R^2, R^3, or R^4 is $NR^5C(O)NHR^8$ may be prepared from compounds of formula I wherein the corresponding substituent is NHR^5 by treatment with the appropriate isocyanate R^8NCO in a suitable solvent, for example tetrahydrofuran.

Compounds of formula I wherein R^2, R^3, or R^4 is $NR^5C(O)OR^9$ may be prepared from compounds of formula I wherein the corresponding substituent is NHR^5 by treatment with an appropriate oxychloride or carbonate in the presence of an optional nucleophilic catalyst, such as 4-(N,N-dimethylamino)pyridine, a base, for example pyridine or triethylamine, and a suitable solvent, for example tetrahydrofuran.

Compounds of formula I wherein R^2, R^3, or R^4 is $NR^5SO_2R^{10}$ may be prepared from compounds of formula I wherein the corresponding substituent is NHR^5 by treatment with an appropriate sulfonyl chloride in a suitable solvent, such as pyridine.

Compounds of formula I wherein R^2, R^3, or R^4 is CN may be prepared from compounds of formula I wherein the corresponding substituent is halide or OSO_2CF_3 by reaction with a cyanide salt, in a suitable solvent, with the addition of a suitable catalyst possibly also

being required. Suitable cyanide salts include copper (I) cyanide, sodium cyanide, sodium dicyanocuprate, or potassium cyanide, and suitable solvents include N,N-dimethylformamide, dimethylsulfoxide, or pyridine. Catalysts which may facilitate the transformation include copper (I) oxide, tetrakis(triphenylphosphine)palladium (0), or nickel (0) complexes generated in situ from dibromobis(triphenylphosphine)nickel(ii), zinc and triphenylphosphine.

Compounds of formula I wherein R^2, R^3 or R^4 is OH, OC_1–C_4 alkyl may be prepared either from an appropriately substituted 2-chloropyridine or via chemical transformation from another substituent e.g; the OH derivative from the NH_2 via the diazo intermediate.

Where necessary, hydroxy, amino, or other reactive groups may be protected using a protecting group as described in the standard text "Protecting Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts.

Compounds of Formula I may be prepared from other compounds of Formula I by using general methods known to one skilled in the art for interconversion of functional groups (see, e.g. the reactions referenced in J. March, "Advanced Organic Chemistry" (1985) 3rd Edition).

Also, several of the substituted compounds of Formula I may be prepared by using an appropriately substituted compound of Formula VIII, viz., 2-chloro-5-trifluoromethylpyridine would yield the R^3 is CF_3.

The above described reactions, unless otherwise noted, are usually conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere). Unless otherwise stated, the above described reactions are conducted under an inert atmosphere, preferably under a nitrogen atmosphere.

The compounds of the invention and intermediates may be isolated from their reaction mixtures by standard techniques.

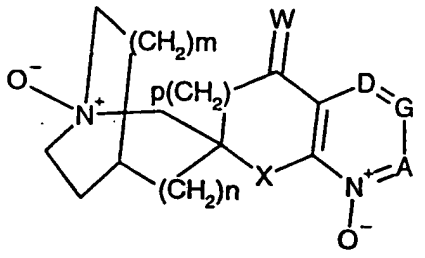
Acid addition salts of the compounds of formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts.

Acid addition salts of compounds of formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

The compounds of formula I exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallization, or chiral HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemization.

(D) Compounds wherein Y is NO

Compounds of formula I, wherein Y is NO, X is oxygen, A is $C(R^2)$, G is $C(R^3)$ and D is $C(R^4)$, may be prepared from compounds of formula XIX, wherein X is oxygen, A is $C(R^2)$, G is $C(R^3)$ and D is $C(R^4)$, by reduction with a suitable reducing agent under suitable conditions, for example sulfur dioxide in ethanol at ambient temperature.



XIX

Compounds of formula XIX may be prepared from compounds of formula I wherein Y is N, X is oxygen, A is $C(R^2)$, G is $C(R^3)$ and D is $C(R^4)$, by oxidation with a suitable oxidising agent under suitable conditions, for example aqueous hydrogen peroxide in acetic acid at reflux temperature.

Compounds of the formula I wherein Y is N, X is oxygen, A is $C(R^2)$, G is $C(R^3)$ and D is $C(R^4)$, may be prepared in analogy with sections (A) , (B) and (C), above.

Compounds of formula I, in which Y is N and A is $C(R^2)$, wherein R^2 is hydroxyl, may be prepared from compounds of formula I in which Y is NO by rearrangement using a carboxylic anhydride in a suitable solvent, for example trifluoroacetic anhydride in DMF;

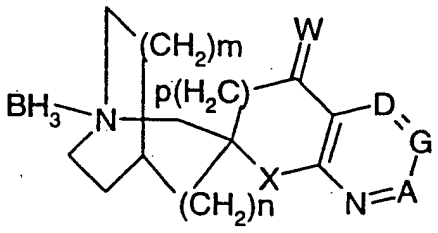
Compounds of formula I in which Y is N and A is $C(R^2)$, wherein R^2 is halogen, may be prepared from compounds of formula I in which Y is NO and A is $C(R^2)$, wherein R^2 is hydrogen, by reaction with a phosphorus halide or oxyhalide, either neat or with a suitable co-solvent, for example neat phosphorus oxychloride.

Compounds of formula I in which Y is N and A is $C(R^2)$, wherein R^2 is CN, may be prepared from compounds of formula I in which Y is NO and A is $C(R^2)$, wherein R^2 is hydrogen, by reaction with a suitable cyanide source such as trimethylsilyl cyanide in the presence of a suitable base, for example triethylamine, in a suitable solvent, for example acetonitrile.

Intermediates

A further aspect of the invention relates to new intermediates. Special interest among these new intermediates are the borane containing compounds, especially the compound of formula II in Scheme I and the compound of formula XIII in Scheme II. These intermediates are useful in the synthesis of compounds of formula I, but their use is not limited to the synthesis of said compounds;

Thus, compounds of the formula II



II

wherein n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

X is oxygen or sulfur;

W is oxygen, H_2 or F_2;

A is N or $C(R^2)$;

G is N or $C(R^3)$;

D is N or $C(R^4)$;

with the proviso that no more than one of A, G, and D is nitrogen;

R^1 is hydrogen or C_1 –C_4 alkyl;

R^2, R^3, and R^4 are independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $–OSO_2CF_3$ or R^2 and R^3, or R^3 or R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the

following substituents: independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R_1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $–OSO_2CF_3$;

R^5 and R^6 are independently hydrogen, C_1–C_4 alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond;

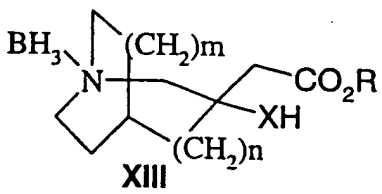
j is 2 to 7;

k is 0 to 2;

R^7, R^8, R^9, R^{10}, and R^{11} are independently C_1–C_4 alkyl, aryl, or heteroaryl,

or an enantiomer thereof .

Compounds of formula XIII



XIII

wherein n is 0 or 1;

m is 0 or 1;

X is oxygen or sulfur;

R^1 is hydrogen or C_1 to C_4 alkyl;

R is C_1–C_6 alkyl, $–CH_2$-Ar, or Ar;

Ar is phenyl optionally substituted with one to three of the following substitutents: halogen, C_1–C_4 alkyl, or C_1–C_4 alkoxy,

or an enantiomer thereof.

Intermediate compounds also exist in enantiomeric forms and may be used as purified enantiomers, racemates or mixtures.

Use of compounds IV, III, II, XIII, X and IX as intermediates in a synthesis of a ligand for nicotinic acetylcholine receptors is another aspect of the invention.

A further aspect of the invention relates to the utility of compounds of formula I wherein Y is NO as intermediates. These intermediates are useful in the synthesis of compounds of formula I wherein Y is N, but their use is not limited to the synthesis of said compounds.

Pharmaceutical compositions

A further aspect of the invention relates to a pharmaceutical composition for treating or preventing a condition or disorder as exemplified below arising from dysfunction of nicotinic acetylcholine receptor neurotransmission in a mammal, preferably a human, comprising an amount of a compound of formula I, an enantiomer thereof or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and an inert pharmaceutically acceptable carrier.

For the above-mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg to about 20 mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of formula I, or an enantiomer thereof, and pharmaceutically acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration. According to a further aspect of the invention, there is provided a pharmaceutical composition including preferably less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture with an inert pharmaceutically acceptable diluent or carrier.

Examples of diluents and carriers are:

– for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose;

– for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Utility

A further aspect of the invention is the use of a compound according to the invention, an enantiomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of one of the below mentioned diseases or conditions; and a method of treatment or prophylaxis of one of the above mentioned diseases or conditions, which comprises administering a therapeutically effective amount of a compound according to the invention, or an enantiomer thereof or a pharmaceutically acceptable salt thereof, to a patient.

Compounds according to the invention are agonists of nicotinic acetylcholine receptors. While not being limited by theory, it is believed that agonists of the α7 nAChR (nicotinic acetylcholine receptor) subtype should be useful in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders, and have advantages over compounds which are or are also agonists of the α4 nAChR subtype. Therefore, compounds which are selective for the α7 nAChR subtype are preferred. The compounds of the invention are indicated as pharmaceuticals, in particular in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders. Examples of psychotic disorders include schizophrenia, mania and manic depression, and anxiety. Examples of intellectual impairment disorders include Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, and Attention Deficit

Hyperactivity Disorder. The compounds of the invention may also be useful as analgesics in the treatment of pain (including chronic pain) and in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, and neurodegenerative disorders in which there is loss of cholinergic synapses. The compounds may further be indicated for the treatment or prophylaxis of jetlag, for use in inducing the cessation of smoking, and for the treatment or prophylaxis of nicotine addiction (including that resulting from exposure to products containing nicotine).

It is also believed that compounds according to the invention are useful in the treatment and prophylaxis of ulcerative colitis.

Pharmacology

The pharmacological activity of the compounds of the invention may be measured in the tests set out below:

Test A - Assay for affinity at α7 nAChR subtype

^{125}I-α-Bungarotoxin (BTX) binding to rat hippocampal membranes. Rat hippocampi were homogenized in 20 volumes of cold homogenization buffer (HB: concentrations of constituents (mM): tris(hydroxymethyl)aminomethane 50; $MgCl_2$ 1; NaCl 120; KCl 5: pH 7.4). The homogenate was centrifuged for 5 minutes at 1000 g, the supernatant was saved and the pellet re-extracted. The pooled supernatants were centrifuged for 20 minutes at 12000 g, washed, and resuspended in HB. Membranes (30–80 μg) were incubated with 5 nM [^{125}I]α-BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM $CaCl_2$ or 0.5 mM EGTA [ethylene glycol-bis(β-aminoethylether)] for 2 hours at 21°C, and then filtered and washed 4 times over Whatman glass fibre filters (thickness C) using a Brandel cell harvester. Pretreating the filters for 3 hours with 1% (BSA/0.01% PEI (polyethyleneimine) in water was critical for low filter blanks (0.07% of total counts per

minute). Nonspecific binding was described by 100 μM (–)-nicotine, and specific binding was typically 75%.

Test B - Assay for affinity to the α4 nAChR subtype

[^{3}H]-(–)-nicotine binding. Using a procedure modified from Martino-Barrows and Kellar (Mol Pharm (1987) 31:169-174), rat brain (cortex and hippocampus) was homogenized as in the [$_{125}$I]α-BTX binding assay, centrifuged for 20 minutes at 12,000 x g, washed twice, and then resuspended in HB containing 100 μM diisopropyl fluorophosphate. After 20 minutes at 4°C, membranes (approximately 0.5 mg) were incubated with 3 nM [3H]-(–)-nicotine, test drug, 1 μM atropine, and either 2 mM $CaCl_2$ or 0.5 mM EGTA for 1 hour at 4°C, and then filtered over Whatman glass fibre filters (thickness C) (pretreated for 1 hour with 0.5% PEI) using a Brandel cell harvester. Nonspecific binding was described by 100 μM carbachol, and specific binding was typically 84%.

Binding data analysis for Tests A and B

IC_{50} values and pseudo Hill coefficients (n_H) were calculated using the non-linear curve fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding K_D values of 1.67 and 1.70 nM for the ^{125}I-α-BTX and [^{3}H]-(–)-nicotine ligands respectively. K_i values were estimated using the general Cheng-Prusoff equation:

$$K_i\text{-}[IC_{50}]/((2+([ligand]/[K_D])_n)_{1/n}\text{-}1)$$

where a value of n=1 was used whenever $n_H<1.5$ and a value of n=2 was used when $n_H\geq1.5$. Samples were assayed in triplicate and were typically±5%. K_i values were determined using 6 or more drug concentrations. The compounds of the invention are compounds with binding affinities (K_i) of less than 1000 nM in either Test A or Test B, indicating that they are expected to have useful therapeutic activity.

The compounds of the invention have the advantage that they may be less toxic, be more efficacious, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

EXAMPLES

Commercial reagents were used without further purification. Mass spectra were recorded using either a Hewlett Packard 5988A or a MicroMass Quattro-1 Mass Spectrometer and are reported as m/z for the parent molecular ion with its relative intensity. Room temperature refers to 20–25°C.

Preparation 1

Spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] N-borane complex

A mixture of trimethylsulfoxonium iodide (16.10 g, 73.2, mmol) and a dispersion of sodium hydride (60% in oil, 3.00 g, 75.0 mmol) in anhydrous dimethyl sulfoxide was stirred at room temperature under nitrogen for 30 minutes. Quinuclidin-3-one (7.05 g, 56.3 mmol) was then added as a solid portionwise, and the resulting mixture was stirred at 65–70°C under nitrogen for 1 hour. The reaction mixture was cooled, water was added (200 mL), and the resulting solution was extracted with chloroform (3 x 200 mL). The chloroform extracts were combined, and back-extracted with water (4 x 200 mL). The chloroform layer was then dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] (6.51 g, 46.8 mmol, 83%) as a clear, colorless liquid. To a stirred solution of spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] (5.3 g, 38.1 mmol) in anhydrous tetrahydrofuran (100 mL) at 0°C was added dropwise a solution of borane in tetrahydrofuran (1.0 M, 38.1 mL, 38.1 mmol), and resulting solution was stirred at 0°C under nitrogen for 30 minutes. Brine (100 mL) was added cautiously to the reaction solution, and the resulting aqueous mixture was extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated

under reduced pressure to afford the title compound (4.3 g, 28.1 mmol, 74%) as a white solid: electrospray MS 152 ([M-H]$^+$, 15).

Preparation 2

3-(2-Chloropyridin-3-ylmethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane N-borane complex

A solution of phenyllithium (1.8 M in cyclohexane/ether [7:3], 167 mL, 0.3 mol, 3 eq.) was added via a cannula to anhydrous tetrahydrofuran (350 mL) at –60°C under a nitrogen atmosphere. Then, diisopropylamine (0.7 mL, 5mmol) was added dropwise, followed by a dropwise addition of 2-chloropyridine (28.4 mL, 0.3 mol, 3 eq.) over ten minutes. The resulting solution was stirred at –40°C under nitrogen for 1.5 hours. The solution was then cooled to –60°C, and a solution of spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] N-borane complex (15.3 g, 0.1 mol) in tetrahydrofuran (75 mL) was added dropwise. The resulting reaction mixture was then stirred at –40°C under nitrogen. After 3 hours, a saturated solution of sodium bicarbonate (150 mL) was slowly added, followed by water (400 mL), and the resulting aqueous mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Column chromatography using silica gel and elution with ethyl acetate/hexanes [3:2] afforded the title compound as a tan solid (17.5 g, 65.6 mmol, 66%): electrospray MS 269 ([MH]$^+$ with ^{37}Cl, 10), 267 ([MH]$^+$ with ^{35}Cl, 26).

Preparation 2(b)

3-(2,4-Dichloropyridin-3-ylmethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane N-borane complex was prepared from 2.64 g (17.8 mmol) of 2,4-dichloropyridine and 1.37 g (8.95 mmol) of spiro[1-azabicyclo[2.2.2]octane-3,2'oxirane], providing 2.42 g (90%), m.p. 178-179°C (1:1 ethyl acetate-hexane).

Preparation 3

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] N-borane complex

3-(2-Chloropyridin-3-ylmethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane N-borane complex (17.4 g, 65.3 mmol) was dissolved in anhydrous N,N-dimethylformamide (500 mL), the

resulting solution was cooled to 0°C under nitrogen, and a dispersion of sodium hydride (60% in oil, 6.55 g, 163 mmol, 2.5 eq.) was added portionwise. The resulting solution was stirred at room temperature under nitrogen for 16 hours. A saturated solution of ammonium chloride (50 mL) was then added at 0°C, followed by ice water (500 mL), and the resulting aqueous mixture was extracted with chloroform (4 x 125 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford an orange solid. Purification through a short column of silica gel eluting with chloroform/acetone [95:5 to 85:15], followed by stirring in hexanes (100mL) and filtration, provided a yellow solid (12.7 g, 55.2 mmol, 84%) of the title compound: electrospray MS 231 ($[MH]^+$, 65).

Preparation 4

3-(2-Methanesulfonyloxyethyl)-3-trimethylsilyloxy-1-azabicyclo[2.2.2]octane N-borane complex

(a) 2-(3-Hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid t-butyl ester

To a solution of diisopropylamine (6.7 mL) in tetrahydrofuran (THF) (20 mL) at 0° C was added n-butyllithium (2.3M in hexanes; 20 mL). The reaction mixture was stirred for 40 minutes and then cooled to –78°C. To this mixture a solution of t-butyl acetate (6.4 mL) in THF (10 mL) was added dropwise and stirring was continued for an additional 15 minutes. Quinuclidin-3-one (5 g) in THF (15 mL) was added to the mixture dropwise and the mixture was allowed to warm to 0°C over 1 hour. To this solution water (100 mL) was added, the solution was extracted twice with chloroform and the combined extracts were washed once with brine. The resulting solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give 9.53 g of the subtitle compound as an off-white solid.

(b) 2-(3-Hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid methyl ester

Trifluoroacetic acid (40 mL) was added dropwise over 15 minutes to a solution of 2-(3-hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid t-butyl ester (15.7 g) in anhydrous dichloromethane (40 mL) at 0°C. The mixture was stirred for 24 hours at room temperature, then the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (90 mL) and cooled in an ice bath. Concentrated sulfuric acid (9 mL)

was added dropwise over 10 minutes, then the reaction mixture was stirred at room temperature. After 3 hours, the solution was poured into 100 mL of ice water, basified to pH 10 with saturated aqueous sodium carbonate solution, and extracted with chloroform (4 x 100 mL). The extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give a solid. Recrystallization from ethyl acetate provided 6.3 g of the tan crystalline subtitle compound.

(c) 2-(3-Hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid methyl ester N-borane complex

Borane in THF (1M, 5.25 mL) was added dropwise over 20 minutes to a solution of 2-(3-hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid methyl ester (1 g) in anhydrous tetrahydrofuran (THF) (20 mL) stirred at 0°C. After 30 minutes, 20 mL of brine was added, stirring was continued for a further 30 minutes and the layers were then separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL), the organic layers were combined, and then dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel (eluting with chloroform/acetone, 95:5) to give the title compound (900 mg) as an off-white solid.

(d) 3-Hydroxy-3-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane N-borane complex

Under an argon atmosphere, lithium borohydride (2M in tetrahydrofuran, 2.6 mL, 5.2 mmol) was added over 5 minutes to a solution of 2-(3-hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid methyl ester N-borane complex (1 g, 4.7 mmol) in anhydrous tetrahydrofuran (20 mL) and heated at reflux for 1 hour. The reaction was cooled (ice bath), quenched with water (5 mL) and saturated aqueous sodium bicarbonate (5 mL), stirred for 45 minutes at 0°C to room temperature, and extracted four times with ethyl acetate. The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure and triturated with ethyl ether to obtain the title compound (830 mg, 4.5 mmol, 95%) as a white solid.

(e) 3-Trimethylsilyloxy-3-(2-trimethylsilyloxyethyl) -1-azabicyclo[2.2.2]octane N-borane complex

Under an argon atmosphere, chlorotrimethylsilane (0.255 mL, 2 mmol) was added via syringe over 5 minutes to 3-hydroxy-3-(2-hydroxyethyl)-1-azabicyclo[2.2.2]octane N-

borane complex (185 mg, 1 mmol) in dry 1-methylimidazole (1 mL) at 0°C. N-(trimethylsilyl)acetamide (262 mg, 2 mmol) was added in one portion, the reaction was stirred for 16 hours at room temperature and heated at 55–60°C for 3 hours. The mixture was cooled, poured into ice/water (5 g), and extracted four times with ether. The combined organic layers were washed four times with brine, dried ($MgSO_4$), evaporated under reduced pressure and purified by flash chromatography (eluting with hexane/ethyl acetate, 3:2) to obtain the title compound (210 mg, 0.64 mmol, 64%).

(f) 3-(2-Hydroxyethyl)-3-trimethylsilyloxy-1-azabicyclo[2.2.2]octane N-borane complex

Under an argon atmosphere, 3-trimethylsilyloxy-3-(2-trimethylsilyloxyethyl) -1-azabicyclo[2.2.2]octane N-borane complex (190 mg, 0.58 mmol) in anhydrous methanol (1mL) containing 0.032 M potassium carbonate in methanol (0.25 mL) was stirred at room temperature for 84 hours, acidified to pH 7 with acetic acid, and evaporated under reduced pressure. Purification by flash chromatography (eluting with hexane/ethyl acetate, 3:2) provided the title compound (94 mg, 0.37 mmol, 63%)

(g) 3-(2-Methanesulfonyloxyethyl)-3-trimethylsilyloxy-1-azabicyclo[2.2.2]octane N-borane complex

Under an argon atmosphere, methanesulfonyl chloride (0.086 mL, 1.1 mmol) in anhydrous pyridine (1 mL) was added over 20 minutes at 0°C – 5°C to a solution of 3-(2-hydroxy-ethyl)-3-trimethylsilyloxy-1-azabicyclo[2.2.2]octane N-borane complex (257 mg, 1 mmol) in anhydrous pyridine (4 mL), stirred at 0°C for 20 minutes, and at room temperature for 2 hours. Poured into ice (15 g), extracted four times with ethyl acetate, combined the organic layers, and washed sequentially with 1 N aqueous hydrochloric acid (three times), water, and saturated aqueous sodium bicarbonate. The extracts were dried ($MgSO_4$), evaporated under reduced pressure and purified by flash chromatography (eluting with chloroform/ethyl acetate, 97:3) to obtain the title compound (263 mg, 0.78 mmol, 78%).

Preparation 5

(a) 3-Ethenyl-3-hydroxy-1-azabicyclo[2.2.2]octane

Under an argon atmosphere, a solution of 3-quinuclidinone (1.25 g, 10 mmol) in anhydrous tetrahydrofuran (10 mL) was added over 15 minutes to a 1 M solution of vinylmagnesium bromide in tetrahydrofuran (20 mL, 20 mmol) at 0°C to 5°C , stirred at room temperature for 24 hours, cooled to 0°C, and acidified to pH 1 with 6 M hydrochloric acid. The mixture was stirred for 15 minutes, basified to pH 10 with 25% aqueous sodium hydroxide, extracted with chloroform (4 x 50 mL) and chloroform/methanol (4:1, 50 mL), combined the organic layers, dried ($MgSO_4$), evaporated under reduced pressure and purified by flash chromatography (eluting with ammoniated chloroform/methanol, 85:15) to obtain the title compound (830 mg, 5.4 mmol, 54%).

(b) 3-Bromo-2-hydroxypyridine

A solution of bromine (9.6 g, 60 mmol) in 1 M aqueous potassium bromide (120 mL) was added over 5 minutes to a solution of 2-hydroxypyridine (5.7 g, 60 mmol) in 1 M aqueous potassium bromide (60 mL) and stirred for 24 hours. The solid precipitate was filtered off, the aqueous phase was saturated with sodium chloride and extracted with chloroform (4 x 20 mL), the combined extracts were dried ($MgSO_4$), evaporated under reduced pressure and combined with the original precipitate. Purification by flash chromatography (eluting with ammoniated chloroform/methanol, 95:5) and recrystallization from acetonitrile provided the title compound (3.62 g, 20.8 mmol, 35%).

(c) 3-Bromo-2-methoxypyridine

Under an argon atmosphere, a mixture of 3-bromo-2-hydroxypyridine (3.49 g, 20 mmol), silver carbonate (3.67 g, 13.31 mmol), and iodomethane (1.5 mL, 24.1 mmol) in benzene (30 mL) was stirred in the dark at 40°C to 50°C for 24 hours, cooled in an ice bath, and filtered. The filtrate was washed once with 2% aqueous sodium bicarbonate and twice with water, dried ($MgSO_4$), the benzene was evaporated at atmospheric pressure, and the residue was purified by flash chromatography (eluting with hexane/ethyl acetate, 2:1) to obtain the title compound (2.35 g, 12.5 mmol, 62%).

Example 1

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

5'-Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] N-borane complex (12.2 g, 53 mmol) was dissolved in 150 mL of acetone, the solution was cooled to 0°C, and an aqueous solution of HBr (24%; 50 mL) was added. The resulting solution was stirred at room temperature under nitrogen for 24 hours. The reaction was concentrated under reduced pressure, and the aqueous residue was treated with saturated aqueous sodium carbonate solution (50 mL). The solution was basified to pH >10 using solid sodium carbonate, and the resulting solution was extracted with chloroform (3 x 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the title compound (11.2 g, 51.8 mmol, 98%, 54% overall) as an off-white solid: electrospray MS 217 ($[MH]^+$, 72).

The title compound was separated into its (R)- and (S)-enantiomers by either of the following methods:

Method A - 250 mg of the title compound was separated by chiral HPLC, using a 2cm X 25cm CHIRALCEL-OD column on a Waters Delta Prep 3000 Preparative Chromatography System, eluting with 2,2,4-trimethylpentane/ethanol (92:8 to 9:1) at a flow rate of 20 mL/min. This provided 111 mg of the (S)-enantiomer ($[\alpha]^{23} = +59.7°$ (c = 1, methanol)) and 90 mg of the (R)-enantiomer ($[\alpha]^{23} = -63.9°$ (c = 1, methanol)).

Method B - 1 g (4.62 mmol) of the title compound was treated with L-(+)-tartaric acid (694 mg; 4.62 mmol) in 15 % aqueous ethanol (10 mL) and recrystallized three times to obtain the (S)-enantiomer L-(+)-tartrate (650 mg; 1.77 mmol; $[\alpha]^{23} = +57.7°$ (c = 2, H_2O)). The filtrates were concentrated under reduced pressure and the aqueous residue was basified to pH >10 using solid sodium carbonate. The resulting mixture was extracted with chloroform (3 x 25 mL) and the combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure. The residue (650 mg; 3 mmol) was treated with D-(–)-tartaric acid (452 mg; 3 mmol) and recrystallized as above to provide the (R)-enantiomer D-(–)-tartrate (775 mg; 2.11 mmol; $[\alpha]^{23} = -58.2°$ (c = 2, H_2O)).

Example 2A

5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution of spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (100 mg, 0.462 mmol) and sodium acetate (410 mg, 5 mmol) in 50 % aqueous acetic acid (4mL) was heated to 60°C. Bromine (0.100 mL, 1.94 mmol) was added via a syringe over 10 minutes, and the solution was then heated under reflux for 1 hour. The mixture was allowed to cool to ambient temperature, basified to pH >10 with sodium carbonate, and extracted with chloroform (3 x 15 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the title compound (110 mg, 0.37 mmol, 81 %) as an off-white solid: electrospray MS 295 ($[MH]^+$, with ^{79}Br, 100), 297 ($[MH]^+$, with ^{81}Br, 98).

Example 2B

(R)-(–)- 5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

The enantiomer (R)-(–)-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (1.95 g, 9 mmol) treated in the same way as described in example 2A provided the title compound (1.77 g, 6 mmol, 67%) ($[\alpha]^{23} = -45.5°$ (c = 1, MeOH)).

Example 3

5'-Phenylspiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Under a nitrogen atmosphere, 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (118 mg, 0.4 mmol), phenylboronic acid (54 mg, 0.443 mmol), and tetrakis(triphenylphosphine)palladium(0) (11 mg, 2.3 mol %) were stirred in a solution of 1,2-dimethoxyethane (3 mL) and ethanol (0.75 mL) containing 2M aqueous sodium carbonate (0.65 mL, 1.3 mmol). The mixture was heated under reflux for 18 hours. The reaction mixture was then evaporated under reduced pressure, the residue was dissolved in chloroform (15 mL), and the extract was washed with saturated aqueous sodium carbonate (5 mL). The aqueous layer was extracted with chloroform (2 x 15 mL), and the organic layers were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Purification by flash chromatography through silica gel, eluting with ammoniated

chloroform/methanol (95:5 to 9:1), provided the title compound (80 mg, 0.274 mmol, 68 %) as a tan solid: electrospray MS 293 ([MH]$^+$, 100).

Example 4A

5'-Nitrospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A mixture of spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (325 mg, 1.5 mmol) and fuming nitric acid (0.27 mL, 5.74 mmol) in sulfuric acid (0.75 mL) was heated at 70°C to 80°C for 24 hours. The resulting viscous solution was poured onto 15 g of ice and basified to pH >10 with solid sodium carbonate. The resulting mixture was extracted with chloroform (4 x 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Purification by flash chromatography through silica gel, eluting with ammoniated chloroform/methanol (95:5), provided the title compound (200 mg, 0.765 mmol, 51 %) as a light yellow solid: electrospray MS 262 ([MH]$^+$, 100).

Example 4B

(R)-(–)-5'-Nitrospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(R)-(–)-Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (3.03 g, 14 mmol) was dissolved in concentrated sulfuric acid (7 mL) at 0 - 5 °C, fuming nitric acid (3.3 mL, 70.2 mmol) was added over 10 minutes, the mixture was stirred for 1 hour, and heated at 65 – 70°C for 24 hours. Cooled, poured onto ice (200 gm), added 300 mL of water, basified to pH 10 with solid potassium carbonate, stirred for 1 hour, filtered off and dried the solid title compound (3.6 g, 13.8 mmol, 98%): electrospray MS (m/z, relative intensity) 262 ([MH]$^+$, 100).

Example 4C

(S)-(+)-5'-Nitrospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

The enantiomer (S)-(+)-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (6.5 g, 30 mmol) treated in the same way as described in example 4B provided the title compound (7.75 g, 29.7 mmol, 99%): electrospray MS (m/z, relative intensity) 262 ([MH]$^+$, 100).

Example 5

Spiro[1-Azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]quinoline]

The title compound was prepared by a procedure analogous to that described in Example 1 from 2-chloroquinoline (0.99 g, 6.06 mmol) and spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] N-borane complex (0.31 g, 2.0 mmol), yielding the title compound (0.135 g) as a beige powder, electrospray MS 267 $[MH]^+$

The two enantiomers were resolved on a Chiral OD column by elution with an 8-10% EtOH/hexane gradient, and UV detection. First enantiomer: 100% chiral purity by LC, Rt = 12.32 minutes, $[\alpha]_D$ at 23° in EtOH = +47.9° . Second enantiomer: 99.4% chiral purity, Rt = 17.84 minutes, $[\alpha]_D$ = -48.5°.

Example 6

1'-Chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]isoquinoline]

The title compound was prepared by a procedure analogous to that described in Example 1 from 1,3-dichloroisoquinoline (2.41 g, 12.2 mmol) and spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] N-borane complex (0.62 g, 4.05 mmol), yielding 0.86 g of 1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]isoquinoline] N-borane complex, electrospray MS 314 $[MH^+]$. Removal of the borane group from 65 mg of the N-borane complex gave 30 mg of the title compound, electrospray MS 301 $[MH^+]$.

Example 7

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]isoquinoline]

The borane protected chloride of Example 6 (0.3g or 0.96 mmol) was suspended in a mixture of glacial acetic acid (6.0 ml) and water (0.5 ml). The suspension was placed under nitrogen and zinc dust (150mg) was added. The reaction mixture was stirred at 70°C for 5 hours. The reaction mixture was allowed to cool and was then poured into saturated $NaHCO_3$. Enough aqueous $NaHCO_3$ was added to give a basic pH, and the products were extracted with three portions of chloroform. The combined chloroform extract was dried ($MgSO_4$), filtered, and evaporated in vacuo. Two runs were combined for purification on a

silica flash column, using a gradient from 2:1 hexane /ethyl acetate to 100% ethyl acetate. The faster eluting compound was spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]isoquinoline] N-borane complex and the slower eluting compound was the title compound. Yield 100%: chemical ionization MS 279 $[MH]^+-H_2$ for the N-borane complex and 267 $[MH]^+$ for the title compound. Removal of the borane group under the conditions of Example 1 followed by flash chromatography gave the title compound as a brown semi-solid: chemical ionization MS 267 $[MH]^+$.

Example 8A

5'-Aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A mixture of 5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (1.4 g, 5.36 mmol), and 10% palladium on carbon (48% water wet, 270 mg) in methanol (90 mL) was hydrogenated for 1 hour at 50 psi of hydrogen. The catalyst was filtered off through a pad of celite and the solvent was evaporated under reduced to obtain the amine (1.2 g, 5.25 mmol, 98%) as a tan solid: electrospray MS (m/z, relative intensity) 232 ($[MH]^+$, 100).

The title compound was separated into its (R)- and (S)- enantiomers by the following method:

150 mg of the title compound was separated by chiral HPLC, using a 2cm X 25cm CHIRALCEL-OD column on a Waters Delta Prep 4000 Preparative Chromatography System [hexane/ethanol (85:15 to 8:2)] at a flow rate of 20 mL/min. This provided 52 mg of the (S)-epimer ($[\alpha]^{22} = +62°$ (c = 1, ethanol) and 52 mg of the (R)-epimer ($[\alpha]^{23} = -64°$ (c = 1, ethanol).

Example 8B

(R)-(–)- 5'-Aminospiro[1-azabicyclo-[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

The enantiomer (R)-(–)-5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (3.8 g, 13.3 mmol) treated in the same way as described in example 8A, and purified by flash chromatography (eluting with ammoniated chloroform/methanol, 95:5 to 85:15), provided the title compound (2.5 g, 10.8 mmol, 81%): electrospray MS (m/z, relative intensity) 232 ($[MH]^+$, 100).

Example 8C

(S)-(+)-5'-Aminospiro[1-azabicyclo-[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

The enantiomer (S)-(+)-5'nitrospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (6.85 g, 26.2 mmol) treated in the same way as described in example 8A in ammoniated methanol provided the title compound (5.55 g, 24 mmol, 92%): electrospray MS (m/z, relative intensity) 232 ($[MH]^+$, 100).

Example 9

5'-Phenylcarboxamidospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Under a nitrogen atmosphere, benzoic acid (67 mg, 0.55 mmol),O-(1H-benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate ("TBTU", 176 mg, 0.55 mmol), 1-hydroxybenzotriazole hydrate ("HOBT", 78 mg, 0.55 mmol), and diisopropylethylamine (0.193 mL, 1.1 mmol) were combined in anhydrous N,N-dimethylformamide (8 mL) and stirred for 10 minutes. 5'-Aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (115 mg, 0.5 mmol) was added as a solid in one portion and stirring was continued for 3 days. The solvent was evaporated under high vacuum to 55°C and the residue was partitioned between saturated aqueous sodium carbonate (2 mL) and dichloromethane (10 mL). After separating, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated under reduced pressure. Purification by flash chromatography through silica gel, eluting with ammoniated chloroform/methanol (9:1), provided the title compound (125 mg, 0.372 mmol, 75 %) as a yellow solid: electrospray MS (m/z, relative intensity) 336 ($[MH]^+$, 100).

Example 10

5'-Phenylaminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] Under a nitrogen atmosphere, phenyl isocyanate (0.056 mL, 0.515 mmol) was added to a suspension of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (119 mg, 0.514 mmol) in anhydrous tetrahydrofuran (5 mL) and stirred for 12 hours. The solvent was evaporated under reduced pressure and the residue purified by flash

chromatography through silica gel, eluting with ammoniated chloroform/methanol (92.5:7.5), to obtain the title compound (155 mg, 0.442 mmol, 86 %) as an off-white solid: electrospray MS (m/z, relative intensity) 351 ([MH]$^+$, 100).

Example 11

5'-Phenylsulfonylamidospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Under a nitrogen atmosphere, benzenesulfonyl chloride (0.07 mL, 0.55 mmol) was added to a solution of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (115 mg, 0.5 mmol) in anhydrous pyridine (5 mL) and stirred for 4 hours. The solvent was evaporated under high vacuum, the residue was partitioned between saturated aqueous sodium carbonate (2 mL) and chloroform (10 mL), separated and extracted the aqueous phase with chloroform (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the residue was re-evaporated from ethanol (3 x 10 mL) under reduced pressure. This afforded the title compound (179 mg, 0.5 mmol, 100%) as a yellow solid: electrospray MS (m/z, relative intensity) 372 ([MH]$^+$, 100).

Example 12

5'-(N-Methylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Under a nitrogen atmosphere, sodium (50 mg, 2.17 mmol) was slowly added (exothermic) to methanol (1 mL) and stirred for 1 hour. 5'-Aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (115 mg, 0.5 mmol) and paraformaldehyde (35 mg, 1.17 mmol) were added and stirred for 16 hours. The reaction was heated at 50°C for 4 hours, sodium borohydride (53 mg, 1.4 mmol) was added, and heated at reflux for 1 hour. Then, 1 N aqueous potassium hydroxide (0.4 mL) was added and continued at reflux for 2 hours more. The solvent was evaporated under reduced pressure, the residue was partitioned between water (1 mL) and chloroform (4 mL), separated and extracted the aqueous phase with chloroform (2 x 4 mL). The combined organic layers were washed with brine (1mL), dried ($MgSO_4$), evaporated under reduced pressure, and purified by flash chromatography through silica gel (eluting with ammoniated chloroform/methanol, 95:5) to obtain the title compound (78 mg, 0.32 mmol, 64%) as an off-white solid: electrospray MS (m/z, relative intensity) 246 ([MH]$^+$, 100).

Example 13A

5'-(N,N-Dimethylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Sodium cyanoborohydride (63 mg, 1 mmol) was dissolved in methanol (2.5 mL), anhydrous zinc chloride (69 mg, 0.5 mmol) was added, stirred for 30 minutes, added the resulting solution to a solution of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (115 mg, 0.5 mmol) and 37% aqueous formaldehyde (0.12 mL, 1.6 mmol) in methanol (2.5 mL), and stirred for 20 hours. Poured into 1 N aqueous potassium hydroxide (10 mL), stirred for 1 hour, evaporated under reduced pressure, and extracted the aqueous residue with chloroform (4 x 10 mL). The combined extracts were dried ($MgSO_4$), evaporated under reduced pressure, and purified by flash chromatography through silica gel (eluting with ammoniated chloroform/methanol, 97.5:2.5), to obtain the title compound (85 mg, 0.33 mmol, 66%) as an off-white solid: electrospray MS (m/z, relative intensity) 260 ($[MH]^+$, 100).

Example 13B

(R)-(–)- 5'-(N,N-Dimethylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

The enantiomer (R)-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (231 mg, 1 mmol) treated in the same way as described in example 13A provided the title compound (178 mg, 0.69 mmol, 69%): electrospray MS (m/z, relative intensity) 260 ($[MH]^+$, 100).

Example 14A

(S)-(+)- 5'-(E)-(Phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution of (S)-(+)- 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (150 mg, 0.51 mmol), styrene (0.07 mL, 0.61 mmol), palladium(II)acetate (1.2 mg, 0.0053 mmol), tri-*o*-tolylphosphine (6.4 mg, 0.021 mmol), and triethylamine (0.5 mL, 3.6 mmol) in anhydrous acetonitrile (0.5 mL), in a heavy-walled threaded glass tube containing a magnetic stir bar, was purged with argon and sealed with a Teflon plug and

FETFE O-ring. The mixture was stirred and heated at 100°C for 2 hours, cooled to room temperature, dissolved in chloroform (10 mL), washed with saturated aqueous sodium carbonate (1 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Recrystallization from ethyl acetate afforded the title compound (90 mg, 0.28 mmol, 55%) as a light tan solid: electrospray MS (m/z, relative intensity) 319 ($[MH]^+$, 100).

Example 14B

(R)-(–)-5'-(E)-(Phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Treatment of the enantiomer (R)-(–)- 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (295 mg, 1 mmol) in the same way as described in example 14A, and purification by flash chromatography (eluting with ammoniated chloroform/methanol, 98:2 to 96:4) provided the title compound (132 mg, 0.41 mmol, 41%): electrospray MS (m/z, relative intensity) 319 ($[MH]^+$, 100).

Example 15 A

(S)-(+)- 5'-(4-Morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Sodium *tert*-butoxide (56.6 mg, 0.59 mmol), tris(dibenzylideneacetone)dipalladium (15.4 mg, 0.017 mmol), and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (21 mg, 0.034 mmol) were combined in a heavy-walled threaded glass tube containing a magnetic stir bar, and purged with argon. Added (S)-(+)- 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (130 mg, 0.44 mmol), morpholine (0.066 mL, 0.76 mmol) and anhydrous tetrahydrofuran (3 mL), sealed with a Teflon plug and FETFE O-ring, stirred and heated at 100°C for 72 hours. The mixture was cooled to room temperature, dissolved in chloroform (25 mL), washed with brine (3 x 2 mL), dried ($MgSO_4$), evaporated under reduced pressure, purified by flash chromatography through silica gel (eluting with ammoniated ether/methanol, 4:1), and recrystallized from ethyl acetate to obtain the title compound (35 mg, 0.12 mmol, 26%) as a tan solid: electrospray MS (m/z, relative intensity) 302 ($[MH]^+$, 100).

Example 15 B

(R)-(–)-5'-(4-Morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Treatment of the enantiomer (R)-(–)-5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (580 mg, 1.965 mmol) in the same way as described in example 15A, provided the title compound (187 mg, 0.62 mmol, 32%): electrospray MS (m/z, relative intensity) 302 ($[MH]^+$, 100).

Example 16

(R)-(–)-5'-(1-Azetidinyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(R)-(–)- 5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (295 mg, 1 mmol), azetidine (0.101 mL, 1.5 mmol), sodium *tert*-butoxide (135 mg, 1.4 mmol), tris(dibenzylideneacetone)dipalladium (46 mg, 0.05 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (62 mg, 0.1 mmol) and anhydrous tetrahydrofuran (9 mL) were combined in a heavy-walled threaded glass tube containing a magnetic stir bar, purged with argon, and sealed with a Teflon plug and FETFE O-ring. The mixture was stirred and heated at 75°C for 4 hours, cooled to room temperature, dissolved in chloroform (20 mL), washed with brine (3 x 10 mL), dried ($MgSO_4$), evaporated under reduced pressure, and purified by flash chromatography through silica gel (eluting with ammoniated chloroform/methanol 95:5) to procure the title compound (230 mg, 0.0.85 mmol, 85%) as a light tan solid: chemical ionization MS (m/z, relative intensity) 272 ($[MH]^+$, 56).

Example 17

(R)-(–)-5'-(2-(4-Pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(R)-(–)-5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (295 mg, 1 mmol), 4-vinylpyridine (0.135 mL, 1.25 mmol), palladium(II)acetate (7.2 mg, 0.032 mmol), tri-*o*-tolylphosphine (38.7 mg, 0.127 mmol), and triethylamine (0.5 mL, 3.6 mmol) in anhydrous acetonitrile (0.5 mL) were combined in a heavy-walled threaded glass tube containing a magnetic stir bar, purged with argon and sealed with a Teflon plug and FETFE O-ring. The mixture was stirred and heated at 100 to 105°C for 48 hours, cooled to room temperature, dissolved in chloroform (25 mL), washed with saturated aqueous sodium

carbonate (2 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Purification by flash chromatography through silica gel (eluting with ammoniated chloroform/methanol, 95:5), followed by recrystallization from acetone afforded the title compound (230 mg, 0.72 mmol, 72%): electrospray MS (m/z, relative intensity) 320 ($[MH]^+$, 100).

Example 18

(R)-(–)-5'-(2-(2-Pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(R)-(–)- 5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (150 mg, 0.5 mmol) was treated with 2-vinylpyridine (0.070 mL, 0.65 mmol) in the same way as described in example 16. Purification by flash chromatography through silica gel (eluting with ammoniated ether/methanol, 95:5 to 9:1), followed by recrystallization from acetonitrile produced the title compound (37 mg, 0.12 mmol, 23%): electrospray MS (m/z, relative intensity) 320 ($[MH]^+$, 100).

Example 19

(R)-(–)-5'-(2-Trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(R)-(–)- 5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine](295 mg, 1 mmol), trimethylsilylacetylene (0.355 mL, 2.5 mmol), tetrakis(triphenylphosphine)palladium (230 mg, 0.2 mmol), triethylamine (2 mL) and anhydrous acetonitrile (2 mL) were combined in a heavy-walled threaded glass tube containing a magnetic stir bar, purged with argon and sealed with a Teflon plug and FETFE O-ring. The mixture was stirred and heated at 100°C for 4 hours, cooled to room temperature, dissolved in chloroform (25 mL), washed with saturated aqueous sodium carbonate (2 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Purification by flash chromatography through silica gel (eluting with ammoniated ether/methanol, 9:1) afforded the title compound (280 mg, 0.90 mmol, 90%): chemical ionization MS (m/z, relative intensity) 313 ($[MH]^+$, 30).

Example 20

(R)-(–)-5'-Ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Under an argon atmosphere, a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.3 mL, 1.3 mmol) was added at 0°C to a solution of (R)-(–)-5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (265 mg, 0.85 mmol) in anhydrous tetrahydrofuran (5 mL), and stirred at room temperature for 2 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (2 mL), extracted with ether (5 x 15 mL), dried ($MgSO_4$), evaporated under reduced pressure, and purified by flash chromatography through silica gel (eluting with ammoniated chloroform/methanol, 95:5) to obtain the title compound (121mg, 0.50 mmol, 59 %): chemical ionization MS (m/z, relative intensity) 241 ($[MH]^+$, 19).

Example 21

5'-(2-Furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution containing 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (103.5 mg, 0.351 mmol), tris(dibenzylidineacetone)dipalladium (0) (14mg, 0.015mmol), tri(o-tolyl)phosphine (44.4 mg, 0.146 mmol), lithium chloride (62mg, 1.46mmol), and 2-(tri-n-butylstannyl)furan (0.17g, 0.476 mmol) in 1,2-dimethoxyethane (1ml) was heated under reflux for 2h. The solution was evaporated, and the residue was taken up in chloroform and filtered. The filtrate was evaporated then purified by HPLC using a gradient of 0–25% 1:1:2 7M methanolic ammonia:methanol:chloroform and chloroform to obtain the title compound (89 mg, 0.313 mmol, 89 %) as a pale solid: electrospray MS (m/z, relative intensity) 283 ($[MH]^+$, 100).

Example 22

5'-(3-Pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution containing 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (158 mg, 0.535 mmol), tris(dibenzylidineacetone)dipalladium (0) (23 mg, 0.025mmol), tri(o-tolyl)phosphine (66 mg, 0.217 mmol), lithium chloride (99 mg, 2.34 mmol), and 3-(tri-n-butylstannyl)pyridine (0.3 ml, approx. 0.3 g, approx. 0.82 mmol) in 1,2-dimethoxyethane (2 ml) was heated under reflux for 6h. The solution was evaporated,

and the residue was taken up in chloroform and filtered. The filtrate was evaporated then purified by HPLC using a gradient of 0-20% 1:1:2 7M methanolic ammonia:methanol:chloroform and chloroform to obtain the title compound (58 mg, 0.198 mmol, 37 %) as a pale solid: electrospray MS (m/z, relative intensity) 294 ($[MH]^+$, 80), 273 (100).

Example 23

5'-Methylspiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2.3-b]pyridine]

A solution containing 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (203 mg, 0.687 mmol), tris(dibenzylidineacetone)dipalladium (0) (33 mg, 0.036 mmol), tri(o-tolyl)phosphine (95 mg, 0.312 mmol), lithium chloride (241 mg, 5.69 mmol), and tetramethylstannane (1.0ml, 1.3g, 7.2 mmol) in 2-methoxyethyl ether (5ml) was heated in a bath maintained at 100°C. After 3h, a further portion of tetramethylstannane (1ml, 1.3g, 7.2mmol) was added, and heating was continued overnight. The solution was filtered, and subjected to purification by HPLC using a gradient of 0–20% 1:1:2 7M methanolic ammonia:methanol:chloroform and chloroform to obtain the title compound (120 mg, 0.519 mmol, 76 %) as a pale solid: electrospray MS (m/z, relative intensity) 231 ($[MH]^+$, 100).

Example 24

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-5'-carbonitrile] and Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-5'-carboxamide]

A solution containing 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (165 mg, 0.558 mmol), and copper (I) cyanide (600mg, 1.3g, approx. 7.2 mmol) in 1-methyl-2-pyrrolidinone (5ml) was heated in a bath maintained at 180 °C overnight and was then allowed to cool. The solution was then partitioned between aqueous ammonia and chloroform, and the organic layer was separated, then dried (magnesium sulfate), filtered, and evaporated. The residue was subjected to purification by HPLC using a gradient of 0-20% 1:1:2 7M methanolic ammonia:methanol:chloroform and chloroform to give spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-5'-carbonitrile] (52 mg, 0.216 mmol, 39 %) as a pale solid: DCI MS (m/z, relative intensity)

242 ([MH]$^+$, 100), and spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-5'-carboxamide] (71 mg, 0.274 mmol, 49 %) as a pale solid: electrospray MS (m/z, relative intensity) 260 ([MH]$^+$, 100).

Example 25

5'-Ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution containing 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (150 mg, 0.508 mmol), tris(dibenzylidineacetone)dipalladium (0) (22mg, 0.024mmol), tri(o-tolyl)phosphine (63mg, 0.206mmol), lithium chloride (103mg, 2.43mmol), and tri-n-butylvinylstannane (188mg, 0.592mmol) in 1,2-dimethoxyethane (10ml) was heated under reflux overnight. The solution was evaporated, and the residue was taken up in chloroform and filtered. The filtrate was evaporated then purified by HPLC using a gradient of 0–25% 1:1:2 7M methanolic ammonia:methanol:chloroform and chloroform to obtain the title compound (93 mg, 0.385 mmol, 76 %) as a pale solid: electrospray MS (m/z, relative intensity) 243 ([MH]$^+$, 100).

Example 26

(R)-(–)-5'-N'-(3-Chlorophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

The (R)-(–)- 5'-Aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (65 mg or 0.28 mmoles) was suspended in 2.7 ml of anhydrous tetrahydrofuran under nitrogen atmosphere. The 3-chlorophenylisocyanate (35 µl) was added and the suspension was stirred at ambient temperature for 5 hours. The tetrahydrofuran was removed in vacuo and the crude was purified by flash chromatography. Elution with 20-40% methanol /chloroform (ammoniated with NH_4OH) gave the desired product spot product. The solvents were removed in vacuo and the residue was taken up in chloroform and dried ($MgSO_4$). Evaporating, chasing with two portions of ether, left 100mg (92%) of white solid. Electrospray MS 385 and 387 [MH]$^+$.

Example 27

(R)-(–)-5'-N'-(2-Nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Using the same method as in example 27 but substituting 2-nitrophenyl isocyanate for 3-chlorophenylisocyanate the title compound was prepared; yield 97 mg (88%) of yellow powder. Electrospray MS 396 $[MH]^+$.

Example 28

(R)-(–)-5'-N,N-Diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Sodium cyanoborohydride (190 mg or 3.0 mmoles) and the zinc chloride (206 mg or 1.5 mmoles) were added to 3.0 mls of anhydrous methanol under nitrogen atmosphere. Stirring for 5 minutes gave complete dissolution. The (R)-(–)- 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (230 mg or 1.0 mmol) was added followed by acetaldehyde (0.335 mls or 6.0 mmoles.) The suspension was stirred at ambient temperature for 16 hours. The methanol was concentrated in vacuo and the suspension was poured into 20 mls of 1 N sodium hydroxide. The aqueous layer was extracted with four 20 ml portions of chloroform, and these were combined dried ($MgSO_4$) and evaporated in vacuo. The crude was purified by flash chromatography, starting with 6/3/1/0.1 ethyl acetate/methanol/water (ammoniated with NH_4OH) and then to 3/6/1/0.1. The solvents were removed in vacuo and the residue was taken up in chloroform and dried ($MgSO_4$.) Obtained 0.227g (79%) of light brown syrup. Electrospray MS 288 $[MH]^+$.

Example 29

(R)-(–)- 5'-N-Ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(R)-(–)- 5'-Aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (230 mg or 1.0 mmoles) and sodium cyanoborohydride were suspended in 6.2 mls of anhydrous methanol. The acetaldehyde (90 µl or 1.1 mmoles) and the solution was stirred at ambient temperature for 16 hours. The methanol was removed in vacuo and the residue was taken up in 2 mls of water and 8 mls of chloroform. The layers were separated and the aqueous layer was extracted 3 times more. The combined organic layers were dried ($MgSO_4$) and

evaporated in vacuo. The crude product was purified by flash chromatography using a 3-15% methanol/chloroform (ammoniated) gradient. The solvents were evaporated in vacuo and chased with two portions of ether. The residue was suspended in ether and collected by filtration. After washing with ether and drying with high vacuum obtained 81 mg (31%) of white powder. Electrospray MS 260 $[\bar{M}H]^+$.

Example 30

(R)-(–)- 5'-N-Benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Prepared by the method of example 12. From 1.0 mmoles obtained 247 mg (77%) of white powder. Electrospray MS 322 $[MH]^+$.

Example 31

(R)-(–)-5'-N-Formamidospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

98% Formic acid (2.1 mls) and acetic anhydride (0.7 mls) were combined under nitrogen atmosphere and cooled with an ice bath. The (R)-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (230 mg or 1.0 mmoles) was added and the reaction was allowed to warm to ambient temperature. The reaction was stirred for 26 hours and then was poured with stirring into saturated sodium carbonate. Solid Na_2CO_3 was added until the pH was basic again, and then the aqueous layer was extracted with four portions of chloroform. These were combined, dried ($MgSO_4$,) and evaporated in vacuo. The crude was purified by flash chromatography eluting with a 2–10% ammoniated methanol/chloroform gradient. The solvents were removed in vacuo and the residue was taken up in chloroform, dried ($MgSO_4$) and evaporated in vacuo. The solvent was chased with two portions of ether giving 0.2g (77%) of white solid. Electrospray MS 260 $[MH]^+$.

Example 32

(R)-(–)- 5'-N-Acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(R)-(–)- 5'-Aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (230 mg or 1.0 mmoles) was dissolved in 3 mls anhydrous pyridine under nitrogen atmosphere. The acetic anhydride (0.1 mls or 1.1 mmoles) was added and the solution was heated at 100°C for 40 hours. The pyridine was removed in vacuo, and the residue was taken up in 8 mls

chloroform and washed with 4 mls of saturated sodium bicarbonate. The aqueous layer was extracted twice more with chloroform and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography using a 3–20% ammoniated methanol/chloroform gradient gave the desired product. The solvents were removed in vacuo and chased with two portions of ether. Obtained 154 mg (56%) of white solid. Chemical ionization MS 274 $[MH]^+$.

Example 33

4'-Chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] and 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[3,2-c]pyridine]

4'-Chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] borane complex and 2'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[3,2-c]pyridine] borane complex were prepared from 2.36 g (7.84 mmol) 3-(2,4-Dichloropyridin-3-ylmethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane N-borane complex and 319 mg (7.97 mmol) of sodium hydride in dimethylformamide as in Preparation 2. This mixture was treated with aqueous hydrobromic acid in acetone to provide, following flash chromatography on neutral silica gel using a mixture of 98:2 ammoniated chloroform/methanol, 559 mg of 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine], m.p. 109-110°C (ethyl ether), and 463 mg of 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[3,2-c]pyridine], m.p. 113-115°C.

Example 34

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[3,2-c]pyridine]

The 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[3,2-c]pyridine] (125 mg or 5.0 mmol) from Example 33 was dissolved in 50 mL of anhydrous methanol, and 25 mg of 10% palladium on carbon was added. The bottle was placed on the Parr apparatus under hydrogen atmosphere and shaken for 2.5 hours. The Pd/C was removed by filtration and washed with methanol. The solvent was removed in vacuo and the residue was taken up in chloroform and methanol and transferred to a vial. The solvent was removed in vacuo and chased with two portions of ether. After drying with high vacuum obtained 112 mg of off-white powder (104% with residual solvent.) Electrospray MS 217 $[MH]^+$

Example 35

4'-Methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Sodium hydride (241 mg, 6.0 mmol) was added to a solution of 76 mg (0.30 mmol) of 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] in 25 mL of ice-cold methanol, under a nitrogen atmosphere. The resulting solution was heated to reflux and stirred for 4 days, then cooled to ambient temperature, poured into 30 mL of water, and extracted with chloroform (3 x 30 mL). The combined organic extract was dried over anhydrous magnesium sulfate, concentrated in vacuo and the residue flash chromatographed on neutral silica gel using a 9:1 mixture of ammoniated chloroform/methanol to give 50 mg (67%) of the title compound as a white solid: electrospray MS (m/z, relative intensity) 247 ($[MH]^+$).

Example 36

4'-Phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

Sodium hydride (151 mg, 3.77 mmol) was added to a solution of 97 mg (0.387 mmol) of 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine], 0.40 mL (3.91 mmol) of thiophenol and 0.10 mL of methanol in 15 mL of dioxane, under a nitrogen atmosphere. The reaction was refluxed for 4 days, cooled to ambient temperature, diluted with 30 mL of water, and extracted with chloroform (3 x 30 mL). The combined organic extract was dried over anhydrous magnesium sulfate, concentrated in vacuo and the residue flash chromatographed on neutral silica gel using a 98:2 mixture of ammoniated chloroform/methanol to give 65 mg (52%) of the title compound as a colourless oil: electrospray MS (m/z, relative intensity) 325 ($[MH]^+$).

Example 37

4'-(N-2-Aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution of 74 mg (0.295 mmol) of 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] in 10 mL of ethylenediamine was heated to reflux under a nitrogen atmosphere and stirred for 4 days. Upon cooling to ambient temperature, the solvent was removed in vacuo. The residue was dissolved in 20 mL of saturated aqueous sodium

carbonate and extracted with chloroform (3 x 25 mL). The combined organic extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to give the title compound as a dark oil, 80 mg (100%): electrospray MS (m/z, relative intensity) 275 ($[MH]^+$).

Example 38

4'-(4-N-Methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution of 97 mg (0.387 mmol) of 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] in 1 mL of 1-methylpiperazine was heated to reflux under a nitrogen atmosphere and stirred for 18 hours. Upon cooling to ambient temperature, the diluted with 40 mL of water, basicified with 2 mL of saturated aqueous sodium carbonate and extracted with chloroform (3 x 25 mL). The combined organic extract was dried over anhydrous magnesium sulfate, concentrated in vacuo, and flash chromatographed on neutral silica gel using a 4:1 mixture of ammoniated chloroform/methanol to provide 59 mg (48%) of the title compound as an amber oil: electrospray MS (m/z, relative intensity) 315 ($[MH]^+$).

Example 39

4'-(Phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution of 97 mg (0.387 mmol) of 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] in 5 mL of benzylamine was heated to reflux under a nitrogen atmosphere and stirred for 18 hours. Upon cooling to ambient temperature, the diluted with 40 mL of water, basicified with 2 mL of saturated aqueous sodium carbonate and extracted with chloroform (3 x 25 mL). The combined organic extract was dried over anhydrous magnesium sulfate, concentrated in vacuo, and flash chromatographed on neutral silica gel using a 9:1 mixture of ammoniated chloroform/methanol to provide 42 mg (34%) of the title compound as a white solid: electrospray MS (m/z, relative intensity) 322 ($[MH]^+$).

Example 40

4'-(Methylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution of 151 mg (0.60 mmol) of 4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] in 25 mL of 40% aqueous methylamine was heated to 175°C in a steel bomb for 18 hours, then cooled to ambient temperature and concentrated in vacuo. The residue was dissolved in 10 mL of ethanol containing 0.4 mL of concentrated hydrochloric acid and the solution was allowed to stand overnight. After filtering, the solution was concentrated in vacuo and the residue crystallized from isopropanol, giving 147 mg of the title compound as a white solid: electrospray MS (m/z, relative intensity) 246 ($[MH]^+$).

Example 41

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide]

A solution of spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (2.88 g, 13.3 mmol) and aqueous hydrogen peroxide (30%, 5 ml) in acetic acid (20 ml) was heated under reflux. After 16 h and 24 h, further portions of hydrogen peroxide were added, and heating was continued for a total of 48 h. The solution was then evaporated, then the residue was redissolved in ethanol (40 ml) which had been saturated with sulfur dioxide. After 4h the solution was evaporated and the residue was purified by HPLC on silica using as the eluant a 0-50% gradient of a mixture of solvents (7 M methanolic ammonia (25%) methanol (25%) chloroform (50%)) and chloroform. The title compound (934 mg,4.0 mmol, 30 %) was a solid: DCI MS 233 ($[MH]^+$).

Example 42

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile]

A solution of spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide] 95 mg, 0.41 mmol) was dissolved in acetonitrile (2 ml). Triethylamine (0.12 ml, 87 mg, 0.86 mmol), and then trimethylsilyl cyanide (0.2 ml, 149 mg, 1.5 mmol) were added. The solution was stirred at room temperature overnight, then heated to reflux temperature. After approx. 8h, further trimethylsilyl cyanide (0.2 ml) was added. After heating under reflux overnight the solution was allowed to cool. Excess methanol was added, and the solution was left at room temperature for 4h then evaporated. The residue was purified by HPLC on

silica using as the eluant a 0-25% gradient of a mixture of solvents (7 M methanolic ammonia (25%) methanol (25%) chloroform (50%)) and chloroform. The title compound (50 mg,0.21 mmol, 51%) was a solid: electrospray MS 242 ($[MH]^+$)

Example 43

6'-Chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

A solution of spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide] (98 mg, 0.42 mmol) in phosphorous oxychloride (2 ml) was heated under reflux for 2h. The solution was evaporated, the residue was partitioned between aqueous potassium carbonate and chloroform, then the organic layer was dried (magnesium sulfate), filtered, and evaporated. The residue was purified by HPLC on silica using as the eluant a 0–25% gradient of a mixture of solvents (7M methanolic ammonia (25%) methanol (25%) chloroform (50%)) and chloroform. The title compound (26 mg, 0.10 mmol, 25 %) was a solid: electrospray MS 251 ($[MH]^+$ with ^{35}Cl) and 253 ($[MH]^+$ with ^{37}Cl).

Example 44

6'-Fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

(a) 6'-Fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] N-borane complex

A solution of phenyllithium (1.8 M in cyclohexane, 13.5 mL) was added to THF (15 mL) under argon. Diisopropylamine (0.5 mL) was added, and the solution was cooled to –78°C (dry ice / acetone bath temperature). To the resulting solution, 2,6-difluoropyridine (1.23 mL, 1.56 g, 13.6 mmol) was added dropwise, then after 1h, a solution of spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] N-borane complex (765 mg, 5.0 mmol) in tetrahydrofuran was added dropwise. The solution was stirred at –78°C for 1h and the cooling bath was then replaced with a dry ice / acetonitrile bath. The solution was then stirred overnight, warming to room temperature. Saturated aqueous sodium bicarbonate was added, and the solution was then extracted with chloroform. The extract was then dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in DMF (20 mL), and was then added to a suspension of hexane-washed sodium hydride (60% mixture with mineral

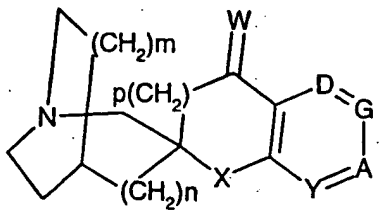
oil, 507 mg, 12.7 mmol) in DMF (20 mL) stirred at 0°C. The solution was stirred overnight, warming to room temperature. Saturated aqueous sodium bicarbonate was added to the solution, which was then extracted with chloroform. The extract was then dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by HPLC using a gradient of 5–50% ethyl acetate and hexane to give the sub-title compound (102 mg, 8%, 0.41 mmol): electrospray MS (m/z) 247 $[M-H]^+$.

(b) 6'-Fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine]

6'-Fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] N-borane complex (98 mg, 0.40 mmol) was dissolved in acetone (5 ml). 48% Aqueous hydrobromic acid (2ml) was diluted with water (2 ml) and then was added to the solution. The resulting mixture was stirred at room temperature overnight. The solution was then evaporated and partitioned between aqueous sodium carbonate and chloroform. The organic extract was then dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by HPLC using a gradient of 0-25% 1:1:2 7M methanolic ammonia:methanol:chloroform and chloroform to give the title compound (39 mg, 0.168 mmol, 43 %) as a solid: electrospray MS (m/z, relative intensity) 235 ($[MH]^+$, 100).

CLAIMS

1. A compound of formula I



I

wherein n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

X is oxygen or sulfur;

Y is CH, N or NO;

W is oxygen, H_2 or F_2;

A is N or $C(R^2)$;

G is N or $C(R^3)$;

D is N or $C(R^4)$;

with the proviso that no more than one of A, G, and D is nitrogen but at least one of Y, A, G, and D is nitrogen or NO;

R^1 is hydrogen or C_1–C_4 alkyl;

R^2, R^3, and R^4 are independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $–OSO_2CF_3$, or R^2 and R^3, or R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substituents: independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$,$–OSO_2CF_3$;

R^5 and R^6 are independently hydrogen, C_1–C_4 alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond;

j is 2 to 7;

k is 0 to 2;

R^7, R^8, R^9, R^{10}, and R^{11} are independently C_1–C_4 alkyl, aryl, or heteroaryl, or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein m is 1.

3. A compound according to any one of claims 1 to 2 wherein n is 0.

4. A compound according to any one of claims 1 to 3 wherein p is 0.

5. A compound according to any one of claims 1 to 4 wherein X is oxygen.

6. A compound according to any one of claims 1 to 5 wherein A is $C(R^2)$; G is $C(R^3)$; and D is $C(R^4)$.

7. A compound according to any one of claims 1 to 6 wherein m is 1; n is 0; p is 0; X is oxygen; A is $C(R^2)$; G is $C(R^3)$; D is $C(R^4)$.

8. A compound according to claim 1, said compound being:
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)- furo[2,3-b]pyridine];
1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline];
5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]; 5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline];
5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(1-azetidinyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carbonitrile];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carboxamide];
5'-N'-(3-chlorophenyl)ureidoaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-N'-(2-nitrophenyl)ureidoaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-Phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-(4-N-methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine];
6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile];
6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];
or an enantiomer, or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 7 in which Y is NO.

10. A compound according to claim 9, being spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide]; or a pharmaceutically acceptable salt, or an enantiomer, thereof.

11. A compound according to any one of claims 1 to 10 for use in therapy.

12. A pharmaceutical composition including a compound as defined in any one of claims 1 to 10, in admixture with an inert pharmaceutically acceptable diluent or carrier.

13. The pharmaceutical composition according to claim 12 for use in the treatment of prophylaxis of human diseases or conditions in which activation of the α7 nicotinic receptor beneficial.

14. The pharmaceutical composition according to claim 12 for use in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

15. The pharmaceutical composition according to claim 12 for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, or mania or manic depression Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for ulcerative colitis.

16. Use of a compound as defined in any one of claims 1 to 10 in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial.

17. The use of a compound as defined in any one of claims 1 to 10, in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

18. The use according to claim 17, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder.

19. The use according to claim 17 wherein the disorder is anxiety, schizophrenia, or mania or manic depression.

20. The use as claimed in claim 17 wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

21. The use of a compound as defined in any of claims 1 to 10, in the manufacture of a medicament for the treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for ulcerative colitis.

22. A method of treatment or prophylaxis of human diseases or conditions in which activation of the $\alpha 7$ nicotinic receptor is beneficial which comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 10.

23. A method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 10.

24. The method as claimed in claim 23, wherein the disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, or Attention Deficit Hyperactivity Disorder.

25. The method as claimed in claim 23, wherein the disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

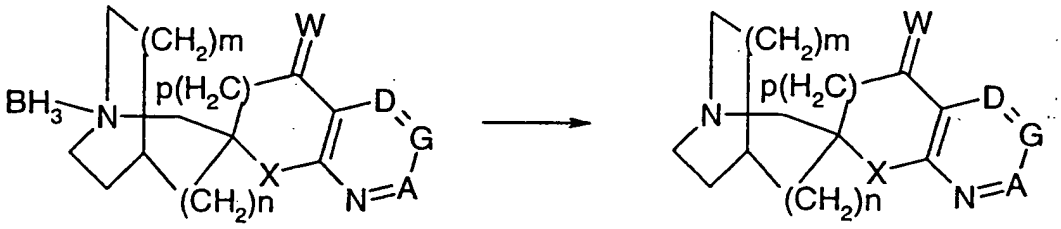
26. The method as claimed in claim 23, wherein the disorder is anxiety, schizophrenia or mania or manic depression.

27. A method of treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction, pain, and for ulcerative colitis which comprises administering a

therapeutically effective amount of a compound as defined in any one of claims 1 to 10.

28. A process for preparation of a compound of formula I, as defined in any of claim 1 to 8, wherein Y is N, or an enantiomer thereof, or a pharmaceutically acceptable salt, which comprises:

removal of a borane complex in a compound of formula II using acid in a suitable solvent or heating the complex in an alcoholic solvent



II I

and when W=F_2 followed by reaction with diethylaminosulfur trifluoride, and where desired or necessary converting the resultant compound of formula I, or enantiomer thereof or an acid addition salt thereof, to a pharmaceutically acceptable acid addition salt thereof, or converting the resultant racemic mixture of the compound of formula I to an enantiomer thereof.

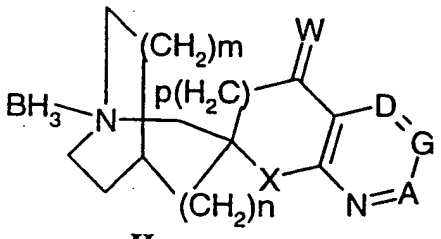
29. A process for the preparation of a compound of the formula I as defined in claim 1, wherein R^1 is hydroxyl and Y is N, by rearrangement of a compound of the formula I as defined in claim 1, wherein Y is NO, using a carboxylic anhydride in a suitable solvent.

30. A process for the preparation of a compound of the formula I as defined in claim 1, wherein R^1 is chloro and Y is N, by rearrangement of a compound of the formula I as

defined in claim 1, wherein Y is NO, using a chlorinating source such as phosphorous oxychloride in a suitable solvent.

31. A process for the preparation of a compound of the formula I as defined in claim 1, wherein R^1 is cyano and Y is N, by rearrangement of a compound of the formula I as defined in claim 1, wherein Y is NO, using a source of cyanide, such as trimethylsilyl cyanide, in a suitable solvent.

32. A compound of the formula



II

wherein n is 0 or 1; m is 0 or 1; p is 0 or 1;

X is oxygen or sulfur;

W is oxygen, H_2 or F_2;

A is N or $C(R^2)$;

G is N or $C(R^3)$;

D is N or $C(R^4)$;

with the proviso that no more than one of A, G, and D is nitrogen;

R^1 is hydrogen or C_1 to C_4 alkyl;

R^2, R^3, and R^4 are independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $–OSO_2CF_3$ or R^2 and R^3, or R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substituents: independently hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, OH, OC_1–C_4 alkyl, CO_2R^1,

–CN, $-NO_2$, $-NR^5R^6$, $-CF_3$,$-OSO_2CF_3$;

R^5 and R^6 are independently hydrogen, C_1–C_4 alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond;

j is 2 to 7;

k is 0 to 2;

R^7, R^8, R^9, R^{10}, and R^{11} are independently C_1–C_4 alkyl, aryl, or heteroaryl;

or an enantiomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01364

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 491/22, A61K 31/435, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 39, 1996, Gunnar Nordvall et al, "3-(2-Benzofuranyl)quinuclidin-2-ene Derivatives: Novel Muscarinic Antagonists", page 3269 - page 3277, Compound 9	1-5,8,11-15
A	WO 9705139 A1 (ABBOTT LABORATORIES), 13 February 1997 (13.02.97)	1-21,28-32
A	WO 9606098 A1 (ASTRA AKTIEBOLAG), 29 February 1996 (29.02.96)	1-21,28-32

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1998	03 -11- 1998
Name and mailing address of the ISA/ Swedish Patent Office	Authorized officer

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01364

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 22-27
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.
PCT/SE 98/01364

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9705139 A1	13/02/97	EP 0842178 A	20/05/98
WO 9606098 A1	29/02/96	AU 690735 B	30/04/98
		AU 3401895 A	14/03/96
		BR 9508751 A	12/08/97
		CN 1159808 A	17/09/97
		CZ 9700392 A	17/12/97
		EP 0777671 A	11/06/97
		FI 970762 A	24/02/97
		GB 9417084 D	00/00/00
		HU 77352 A	30/03/98
		IL 115039 D	00/00/00
		JP 10504561 T	06/05/98
		PL 318760 A	07/07/97
		SK 21697 A	10/09/97
		ZA 9507122 A	18/04/96
		GB 9504627 D	00/00/00
		NO 970800 A	21/02/97

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant (*for all designated States except US*): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): LOCH, James, III [US/US]; Astra Arcus USA, Inc., P.O. Box 20890, Rochester, NY 14603 (US). MULLEN, George [US/US]; Astra Arcus USA, Inc., P.O. Box 20890, Rochester, NY 14603 (US). PHILLIPS, Eifion [GB/US]; Astra Arcus USA, Inc., P.O. Box 20890, Rochester, NY 14603 (US).

(74) Agent: ASTRAZENECA AB; Intellectual Property, Patents, S-151 85 Södertälje (SE).

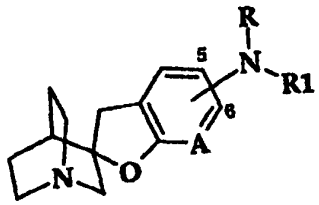
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL ARALKYL AMINES OF SPIROFUROPYRIDINES USEFUL IN THERAPY



(I)

(57) Abstract

A compound of formula (I), wherein NRR_1 is attached at the 5- or 6-position of the furopyridine ring; R is hydrogen, C_1–C_4 alkyl, or COR_2; R_1 is $(CH_2)_nAr$, $CH_2CH{=}CHAr$, or $CH_2C{\equiv}CAr$; n is 0 to 3; A is N or NO; Ar is a 5- or 6-membered aromatic or heteroaromatic ring which contains zero to four nitrogen atoms, zero to one oxygen atom, and zero to one sulfur atoms; or an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing zero to four nitrogen atoms, zero to one oxygen atoms, and zero to one sulfur, any of which may optionally be substituted with one to two substituents independently selected from: halogen, trifluoromethyl, or C_1–C_4 alkyl; or substituted with one to three of the following substituents: halogen, R_2 is hydrogen, C_1–C_4 alkoxy or phenyl ring optionally may be hydrogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH; OC_1–C_4 alkyl, CO, –NO_2, –NR_3R_4, or –CF_3; R_3, R_4 are following substituents: halogen, C_1–C_4 alkyl, or phenyl optionally substituted with one to three thereof, processes for preparing them, compositions containing them, and their use in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders.

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NOVEL ARALKYL AMINES OF SPIROFUROPYRIDINES USEFUL IN THERAPY

TECHNICAL FIELD

This invention relates to novel substituted amines of spirofuropyridines or pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy. A further object is to provide active compounds, which are potent ligands for nicotinic acetylcholine receptors (nAChR's).

BACKGROUND OF THE INVENTION

The use of compounds which bind nicotinic acetylcholine receptors in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease has been discussed in McDonald et al. (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; Williams et al. (1994) "Neuronal Nicotinic Acetylcholine Receptors," Drug News & Perspectives, vol. 7, pp. 205-223; and Lin and Meyer, "Recent Developments in Neuronal Nicotinic Acetylcholine Receptor Modulators", Exp. Opin. Ther. Patents. (1998), 8(8): 991-1015.

US Patent 5,468,875 discloses N-alkylcarbamic acid 1-azab[illegible]o [2.2.1]hept-3-yl esters which are centrally active [illegible]carinic agents useful in the tr[illegible]t of Alzheimer's disease and other disorders.

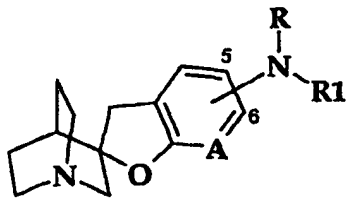
N-(2-alkoxyphenyl) carba[illegible]cid 1-azabicyclo[2.2.2]octan[illegible]ters are disclosed in Pharmazie, vol. 48, 465-[illegible]993) along with their local a[illegible]c activity. N-

phenylcarbamic acid 1-azabicyclo [2.2.2]octan-3-yl esters substituted at the *ortho* position on the phenyl ring are described as local anaesthetics in *Acta Pharm. Suecica*, 7, 239-246 (1970).

Furopyridines useful in controlling synaptic transmission are disclosed in WO 97/05139.

DISCLOSURE OF THE INVENTION

According to the invention it has been found that compounds of formula I,



I

wherein

NRR_1 is attached at the 5- or 6-position of the furopyridine ring;

R is hydrogen, C_1-C_4 alkyl, COR_2;

R_1 is $(CH_2)_nAr$, $CH_2CH=CHAr$, or $CH_2C\equiv CAr$;

n is 0 to 3;

A is N or NO;

Ar is a 5- or 6-memb aromatic or heteroaromatic h contains zero to four nitrogen atoms, zero oxygen atoms, and zero to ur atoms;

or an 8-, 9- or 10-m d fused aromatic or heterc ing system containing zer to four nitrogen ato to one oxygen atoms, an ie sulfur atoms; any of

which may optionally be substituted with one to two substitutents independently selected from: halogen, trifluoromethyl, or C_1-C_4 alkyl;

R_2 is hydrogen, C_1-C_4 alkyl; C_1-C_4 alkoxy; or phenyl ring optionally substituted with one to three of the following substituents: halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH; OC_1–C_4 alkyl, CO_2R_5, –CN, $–NO_2$, $–NR_3R_4$, or $–CF_3$;

R_3, R_4 and R_5 are independently hydrogen; C_1-C_4 alkyl; or phenyl ring optionally substituted with one to three of the following substituents: halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH, OC_1–C_4 alkyl, CO_2R_2, –CN; $–NO_2$, or $–CF_3$;

or an enantiomer thereof, and pharmaceutically acceptable salts thereof, are potent ligands for nicotinic acetylcholine receptors.

Unless otherwise indicated, the C_1–C_4 alkyl groups referred to herein, e.g., methyl, ethyl, n-propyl, n-butyl, i-propyl, i-butyl, t-butyl, s-butyl, may be straight-chained or branched, and the C_3–C_4 alkyl groups may also be cyclic, e.g., cyclopropyl, cyclobutyl.

Unless otherwise indicated, the C_1–C_4 alkoxy groups referred to herein, e.g., methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, s-butoxy, may be straight-chained or branched.

Unless otherwise indicated, the C_2–C_4 alkenyl groups referred to herein may contain one or two double bonds, e.g., ethenyl, i-propenyl, n-butenyl, i-butenyl, allyl, 1,3-butadienyl.

Unless otherwise indicated, the C_2–C_4 alkynyl groups referred to herein contain one triple bond, e.g., ethynyl, 1-propynyl, 1- or 2-butynyl.

Halogen referred to herein may be fluoride, chloride, bromide, or iodide.

Unless otherwise indicated, (subst)phenyl refers to a phenyl ring optionally substituted with one to three of the following substituents: hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH, OC_1–C_4 alkyl, CO_2R_5, –CN, $–NO_2$, $–NR_3R_4$, $–CF_3$.

Preferred compounds of the invention are compounds of formula I wherein A is N.

Preferred compounds of the invention are compounds of formula I wherein R_1 is $(CH_2)_nAr$.

Preferred compounds of the invention are compounds of formula I wherein R_1 is $CH_2CH=CHAr$.

Preferred compounds of the invention are compounds of formula I wherein R_1 is $CH_2C\equiv CAr$.

Preferred compounds of the invention are compounds of formula I wherein Ar is selected from the group: phenyl ring optionally substituted with one to three of the following substituents: halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH, OC_1–C_4 alkyl, CO_2R_5, –CN, $–NO_2$, $–NR_3R_4$, and $–CF_3$; 2-, 3-, or 4-pyridyl; 2-, or 3-furanyl; 2-, or 3-thienyl; 2-, or 4-imidazolyl; 1, 2-, or 3-pyrrolyl; 2-, or 4-oxazolyl; and 3-, or 4-isoxazolyl.

Preferred compounds of the invention are compounds of formula I wherein Ar is selected from the group: 1-, or 2-naphthyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl; 2-, 4-, 5-, 6-, or 7-benzoxazolyl; and 3-, 4-, 5-, 6-, or 7-benzisoxazolyl.

Pr[illegible]d compounds of the invention are compounds of formula I, wh[illegible] R_3, R_4 and R_5 a[illegible]endently hydrogen, or C_1-C_4 alkyl.

P[illegible] compounds of the invention[illegible] compounds of formula I wh[illegible] is 1.

Preferred compounds of the invention are compounds of formula I wherein R is hydrogen.

Preferred compounds of the invention are compounds of formula I wherein Ar is an heteroaromatic ring.

Preferred compounds of the invention are compounds of formula I wherein n is 1, R is hydrogen and Ar is an heteroaromatic ring.

Preferred compounds of the invention include the following:

R-(–)-5'-N-(Phenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-(2-Pyridylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-(3-Pyridylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-(4-pPyridylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-(2-Furanylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-(3-Furanylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-(2-Thienylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-(2-Imidazolylmethyl) aminospiro[1-azabicyclo[2.2.2]oct[illegible]ne-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(4-Methoxyphenylmethyl) aminospiro[1-azabicyc[illegible].2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(4-Chlorophenyl[illegible]yl) aminospiro[1-azabicycl[illegible]ctane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(4-Methylphenyl[illegible]yl) aminospiro[1-azabicycl[illegible]ctane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3,4-Dichlorophenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Acetyl- N-(phenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Methyl-N-(phenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Pyridyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];

R-(–)-6'-N-(Phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(2-Phenylethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Phenylpropyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(Quinolin-3-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(Quinolin-4-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(1,4-Benzodioxan-6-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(Imidazol-4-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(*tran*[illegible]henylprop-2-enyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridi[illegible]

R-(–)-5'-N-(Thi[illegible]ylmethyl)aminospiro[1-azab[illegible]lo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyrid[illegible]

R-(–)-5'-N-(3-N[illegible]nylmethyl)aminospiro[1-[illegible]cyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyrid[illegible]

R-(–)-5'-N-(2-Chlorophenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Chlorophenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Phenylpropynyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Hydroxyphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(4-Hydroxyphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-[*trans*-3-(4-Pyridinyl)prop-2-enyl]aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Acetyl-N-(3-Thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Methyl-N-(4-pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Methyl-N-(3-pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(2-Hydroxyethyl)-N-(3-thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

and enantiomers thereof, and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of the invention are compounds of formula I wherein n is 1; R is hydrogen and Ar is an heteroaromatic ring, including the following compounds:

R-(–)-5'-(3-[illegible]ylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

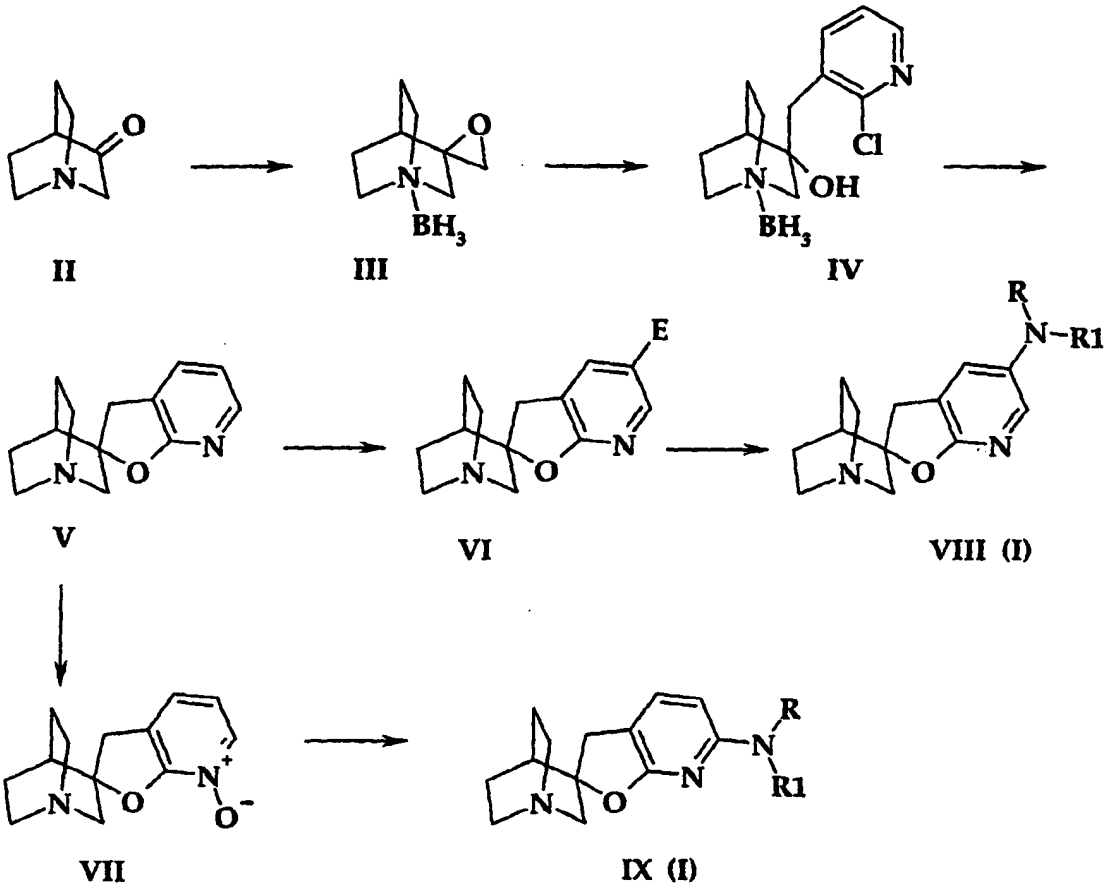
R-(–)-5'-(4-[illegible]ylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

and enantiomers thereof, and pharmaceutically acceptable salts thereof.

The compounds of the invention have the advantage that they may be less toxic, be more efficacious, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

Methods of Preparation

In the reaction schemes and text that follow, R and R_1, unless otherwise indicated, are as defined above for formula I. Formula VIII represents a compound of formula I wherein NRR_1 is attached at the 5-position of the furopyridine ring. Formula IX represents a compound of formula I wherein NRR_1 is attached at the 6-position of the furopyridine ring. A represents N; E represents halogen, NO_2, or NHR. The compounds of formula I may be prepared according to the methods outlined in Scheme 1.



Scheme 1.

Compounds of formula I wherein A represents NO may be prepared from compounds of formula I wherein A represents N by oxidation with a peroxidic reagent in a suitable solvent, followed by reduction of the tertiary amine oxides in a suitable solvent. Oxidizing agents include hydrogen peroxide, m-chloroperbenzoic acid, peracetic acid, or magnesium monoperoxyphthalate. The preferred oxidant is m-chloroperbenzoic acid. Suitable inert solvents include chloroform, methylene chloride, and 1,2-dichloroethane. The preferred solvent is dichloromethane. The reaction is usually conducted at a temperature from 0°C to 66°C, preferably from 0°C. Reducing agents include sulfur dioxide and triphenylphosphine. The preferred reagent is sulfur dioxide. Suitable solvents include

water and alcohols. The preferred solvent is ethanol. The reaction is usually conducted at a temperature from -20°C to 50°C, preferably from 0°C to 25°C.

Compounds of formula I wherein R represents COR_2 may be prepared from compounds of formula I wherein R represents hydrogen using a suitable acylation procedure. Typical acylation procedures include treatment with a carboxylic acid and a coupling agent, for example dicyclohexylcarbodiimide, in a suitable solvent, for example tetrahydrofuran, or treatment with a carboxylic acid chloride or anhydride in the presence of a base. The preferred method is treatment with a carboxylic anhydride. Suitable bases include triethylamine, 4-(N,N-dimethylamino)pyridine, or pyridine. The preferred base is pyridine. The reaction is usually conducted at a temperature of 0°C to 120°C, preferably from 80°C to 100°C.

Compounds IX may be prepared from compound VII by reaction with a halogenating reagent such as phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride or phosphorus pentabromide, followed by reaction with an amine in an inert solvent. The preferred halogenating agent is phosphorus oxychloride. The halogenating reaction is usually conducted at a temperature from 0°C to 150°C, preferably from 80°C to 120°C. The amine component may be any amine $NHRR_1$ defined as above. Suitable inert solvents include alcoholic solvents such as methanol and ethanol, as well as aromatic solvents such as benzene, toluene or xylene. The preferred inert solvent is ethanol. The reaction is usually conducted at a temperature from 20°C to 200°C, preferably from 100°C to 170°C. The reaction with the amine may be facilitated by the presence of a suitable organometallic catalyst and a base. Suitable organometallic catalysts include palladium phosphine complexes, which may be formed *in situ* from a source of palladium and a suitable phosphine. The preferred source of palladium is tris(dibenzylidineacetone)dipalladium (0). The preferred phosphine is 2-2'-bis(diphenylphosphino)-1-1'-binaphthyl. Suitable bases include lithium bis(trimethylsilyl)amide, sodium t-butoxide, preferably potassium t-butoxide. Suitable inert solvents for the reaction in the presence of an organometallic catalyst include tetrahydrofuran, 1,2-dimethoxyethane, or 1,4-dioxane, preferably 1,2-dimethoxyethane,

and the reaction is usually conducted at a temperature of 60°C to 120°C, preferably from 80°C to 110°C.

Compounds of formula VIII may be prepared from compounds of formula VI wherein E represents NHR by a suitable alkylation procedure. Typical alkylation procedures include treatment with an appropriate alkyl halide or sulfonate ester and base, for example sodium hydride, in a suitable solvent, for example DMF, or reductive alkylation using the appropriate aromatic aldehyde together with a suitable reducing agent in an inert solvent. The preferred method is reductive alkylation. Suitable aromatic aldehydes include $Ar(CH_2)_mCHO$, ArCH=CHCHO, or ArC≡CCHO, where m may be 0 - 2 and Ar is defined as above. Suitable reductive alkylating agents include sodium borohydride and sodium cyanoborohydride. The preferred reducing agent is sodium borohydride. Suitable inert solvents include water, methanol or ethanol. The preferred solvent is methanol. The reaction is usually conducted at a temperature of 0°C to 100°C, preferably from 20°C to 65°C.

Compounds of formula VIII may be prepared from compounds of formula VI wherein E represents halogen by reaction with an amine of formula RR_1NH in the presence of a suitable organometallic catalyst, base, and solvent. Suitable organometallic catalysts include palladium phosphine complexes, which may be formed in situ from a source of palladium and a suitable phosphine. The preferred source of palladium is tris(dibenzylidineacetone)dipalladium (0). The preferred phosphine is 2-2'-bis(diphenylphosphino)1,1'-binaphthyl. Suitable bases include lithium bis(trimethylsilyl)amide, or sodium t-butoxide, preferably sodium t-butoxide. Suitable inert solvents include tetrahydrofuran, 1,2-dimethoxyethane, or 1,4-dioxane. The preferred solvent is 1,2-dimethoxyethane. The reaction is usually conducted at a temperature of 60°C to 120°C, preferably from 80°C to 110°C.

Compound VII may be prepared from compound V by oxidation with a peroxidic reagent in a suitable solvent followed by reduction of the tertiary amine oxides in a suitable solvent. Oxidizing agents include hydrogen peroxide, m-chloroperbenzoic acid per-

acid, or magnesium monoperoxyphthalate. The preferred oxidant is m-chloroperbenzoic acid. Suitable inert solvents include chloroform, methylene chloride, and 1,2-dichloroethane. The preferred solvent is dichloromethane. The reaction is usually conducted at a temperature from -20°C to 66°C, preferably from 0°C to 20°C. Reducing agents include sulfur dioxide and triphenylphosphine. The preferred reagent is sulfur dioxide. Suitable inert solvents include water and alcohols. The preferred solvent is ethanol. The reaction is usually conducted at a temperature from -20°C to 50°C, preferably from 0°C to 25°C.

Compounds of formula VI wherein E represents NHR and R represents an alkyl group may be prepared from compounds of formula VI wherein E represents NH_2 by a suitable alkylation procedure. Typical alkylation procedures include treatment with an appropriate alkyl halide or sulfonate ester and base, for example sodium hydride, in a suitable solvent, for example DMF, or reductive alkylation using the appropriate aldehyde or ketone together with a suitable reducing agent in an inert solvent. The preferred method is reductive alkylation. Suitable reducing agents include sodium borohydride and sodium cyanoborohydride. The preferred reducing agent is sodium borohydride. Suitable inert solvents include water, methanol or ethanol. The preferred solvent is methanol. The reaction is usually conducted at a temperature of 0°C to 100°C, preferably from 20°C to 65°C.

Compounds of formula VI wherein E represents NH_2 may be prepared from compounds of formula VI wherein E represents NO_2 by reduction in a suitable solvent. Suitable reducing agents include hydrogen in the presence of a catalyst, for example 5-10% palladium on carbon, platinum oxide, or rhodium on carbon. The preferred reducing agent is hydrogen in the presence of 5% palladium on carbon. Suitable inert solvents include water, methanol or ethanol. The preferred solvent is methanol. The reaction is usually conducted at a temperature of 15°C to 65°C, preferably 15°C

Compound VI wherein E represents NO_2 may be prepared from compound V by reaction with a nitrating agent in an appropriate solvent. The preferred nitrating agent is fuming nitric acid; the preferred solvent is sulfuric acid. The reaction is usually conducted at a temperature from -10°C to 100°C, preferably from 50°C to 80°C.

Compounds of formula VI wherein E represents halogen may be prepared from a compound V by reaction with a halogenating agent in a suitable solvent, for example bromine in acetic acid. The reaction is usually carried out at a temperature of 0°C to 110°C, preferably from 60°C to 110°C.

Compound V may be prepared from the cyclization of compound IV in the presence of a base in an inert solvent, followed by deprotection of the cyclized compound using acid in a suitable solvent. Suitable bases include sodium hydride, sodium amide, potassium hydride, potassium *t*-amylate, potassium *t*-butoxide, and potassium bis(trimethylsilyl)amide. The preferred base is sodium hydride. Suitable inert solvents include N,N-dimethylformamide, N-methylpyrrolidin-2-one, ethers such as diethyl ether, tetrahydrofuran, and 1,4-dioxane, and dimethylsulfoxide. The preferred inert solvent is N,N-dimethylformamide. The reaction is usually conducted at a temperature from −10°C to 100°C, preferably from 20°C to 66°C.

Suitable acids for the deprotection of the cyclized compound include mineral, organic and Lewis acids, for example, hydrochloric and hydrobromic acid, sulfuric acid, triflic acid, methanesulfonic acid, and boron trifluoride etherate. The preferred acid is hydrobromic acid. Suitable solvents include acetone, butanone, ethanone, and pinacolone. The preferred solvent is acetone. The reaction is usually conducted at a temperature from −10°C to 100°C, preferably from 0°C to 60°C. Alternatively the deprotection may be conducted by heating a borane complex in alcoholic solvents. A preferred method is by refluxing an ethanolic solution of the complex.

Compound V may be prepared from compound III using a lithium base and a proton transfer agent in an inert solvent. Suitable lithium bases include lithium diisopropylamide,

n-butyllithium, *sec*-butyllithium, *tert*-butyllithium, and phenyllithium. The preferred lithium base is phenyllithium. Suitable proton transfer agents include hindered secondary amines such as diisopropylamine and 2,2,6,6-tetramethylpiperidine. The preferred proton transfer agent is diisopropylamine. Suitable inert solvents include diethyl ether, tetrahydrofuran and 1,4-dioxane. The preferred inert solvent is tetrahydrofuran. The reaction is usually conducted at a temperature from −100°C to 0°C, preferably from −78°C to −25°C.

Compound III may be prepared from the reaction of compound II with an anion of a reagent well known in the art for the preparation of oxiranes from ketones (see e.g. the reactions referenced in J. March, "Advanced Organic Chemistry" (1992) 4th Edition, pages 974-975), followed by reaction with borane (BH_3 or B_2H_6) in an inert solvent, Borane in tetrahydrofuran is preferred. Suitable inert solvents include diethyl ether, tetrahydrofuran and 1,4-dioxane. The preferred inert solvent is tetrahydrofuran. The reaction is usually conducted at a temperature from −10°C to 66°C, preferably from 0°C to 20°C. Suitable epoxidizing agents include trimethylsulfoxonium iodide, trimethylsulfonium iodide and diazomethane. The preferred reagent is trimethylsulfoxonium iodide. Suitable inert solvents include dipolar aprotic solvents. The preferred solvent is dimethylsulfoxide. The reaction is usually conducted at a temperature from −10°C to 100°C, preferably from 50°C to 75°C.

Where necessary, hydroxy, amino, or other reactive groups may be protected using a protecting group as described in the standard text "Protecting groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts.

The above described reactions, unless otherwise noted, are usually ucted at a pressure one to three atmospheres, preferably at ambient pressure (about mosphere). Unless erwise stated, the above-desc d reactions are conducted und ert atmosphere, ferably under a nitrogen atmc re.

The compounds of the invention and intermediates may be isolated from their reaction mixtures by standard techniques.

Acid addition salts of the compounds of formula I which may be mentioned include salts of mineral acids, for example the hydrochloride and hydrobromide salts; and salts formed with organic acids such as formate, acetate, maleate, benzoate, tartrate, and fumarate salts.

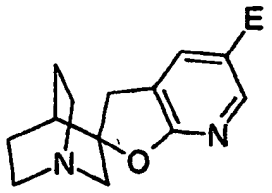
Acid addition salts of compounds of formula I may be formed by reacting the free base or a salt, enantiomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g., water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed in vacuum or by freeze drying. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

The compounds of formula I exist in tautomeric or enantiomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, e.g. fractional crystallization, or chiral HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemization.

Intermediates

A further aspect of the ...ation relates to new interme... pecial interest among these new intermediates are ...mpounds of formula VI ar... Scheme I. These intermediates are use... ...e synthesis of compounds ...a I, but their use is not limited to the synthes... ...l compounds. The formu... ...e compounds are presented below:

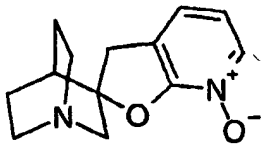
Compounds of formula VI



VI

where E is NO_2, NHR or halogen;

and compounds of formula VII



VII

Intermediate compounds also exist in enantiomeric forms and may be used as purified enantiomers, racemates or mixtures.

Use of compounds VI and VII as intermediates in a synthesis of a ligand for nicotinic acetylcholine receptors is another aspect of the invention.

Pharmaceutical compositions

A further aspect of the invention relates to a pharmaceutical composition for treating or preventing a condition or disorder as exemplified below arising from dysfunction of nicotinic cholinergic neurotransmission in a mammal, preferably a human, comprising an amount of a compound of formula I or an enantiomer thereof, and a

pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and an inert pharmaceutically acceptable carrier.

For the above-mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results will be obtained when the compounds of the invention are administered at a daily dosage of from 0.1 mg to 20 mg per kg of mammalian body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of formula I, or an enantiomer thereof, and pharmaceutically acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral, parenteral, oral, rectal or nasal administration. According to a further aspect of the invention, there is provided a pharmaceutical composition preferably comprising less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture with an inert pharmaceutically acceptable diluent or carrier.

Examples of suitable diluents and carriers are:

– for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose;

– for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

There is also provided a process for the preparation of such a pharmaceutical composition, which comprises mixing the ingredients simultaneously or sequentially.

Utility

A further aspect of the invention is the use of a compound according to the invention, or an enantiomer thereof, and a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of one of the below mentioned diseases or conditions; and a method of treatment or prophylaxis of one of the below mentioned diseases or conditions, which comprises administering a therapeutically effective amount of a compound according to the invention, or an enantiomer thereof, and a pharmaceutically acceptable salt thereof, to a patient.

Compounds according to the invention are agonists of nicotinic acetylcholine receptors. While not being limited by theory, it is believed that agonists of the α7 nAChR (nicotinic acetylcholine receptor) subtype should be useful in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders, and have advantages over compounds which are, or are also agonists of the α4 nAChR subtype. Therefore, compounds which are selective for the α7 nAChR subtype are preferred. The compounds of the invention are selective for the α7 nAChR subtype. The compounds of the invention are intended as pharmaceuticals, in particular in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders. Examples of psychotic disorders include schizophrenia, mania or manic depression, and anxiety. Examples of intellectual impairment disorders include Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Lewy Body Dementia, and Attention Deficit Hyperactivity Disorder. The compounds of the invention may also be useful as analgesics in the treatment of pain (including chronic pain) and in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, and neurodegenerative disorders in which there is loss of cholinergic synapses. The compounds may further be indicated for the treatment or prophylaxis of jetlag, for use in inducing the cessation of smoking and for the treatment or prophylaxis of nicotine addiction (including that resulting from exposure to products containing nicotine).

It is also believed that compounds according to the invention are useful in the treatment and prophylaxis of ulcerative colitis.

Pharmacology

The pharmacological activity of the compounds of the invention may be measured in the tests set out below:

Test A - Assay for affinity at α7 nAChR subtype

^{125}I-α-Bungarotoxin (BTX) binding to rat hippocampal membranes. Rat hippocampi were homogenized in 20 volumes of cold homogenization buffer (HB: concentrations of constituents (mM): tris(hydroxymethyl)aminomethane 50; $MgCl_2$ 1; NaCl 120; KCl 5: pH 7.4). The homogenate was centrifuged for 5 minutes at 1000 x g, the supernatant was saved and the pellet re-extracted. The pooled supernatants were centrifuged for 20 minutes at 12,000 x g, washed, and resuspended in HB. Membranes (30–80 μg) were incubated with 5 nM [^{125}I]α-BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM $CaCl_2$ or 0.5 mM EGTA [ethylene glycol-bis(β-aminoethylether)] for 2 hours at 21°C, and then filtered and washed 4 times over Whatman glass fibre filters (thickness C) using a Brandel cell harvester. Pretreating the filters for 3 hours with 1% (BSA/0.01% PEI (polyethyleneimine)) in water was critical for low filter blanks (0.07% of total counts per minute). Nonspecific binding was described by 100 μM (–)-nicotine, and specific binding was typically 75%.

Test B - Assay for affinity to the α4 nAChR subtype

[^{3}H]-(–)-nicotine binding. Using a procedure modified from Martino-Barrows and Kellar (Mol Pharm (1969-174), rat brain (cortex and hippocampus) was homogenized in the [^{125}I]α-BTX binding assay, centrifuged for 20 minutes at 12,000 x g, washed twice and then resuspended in HB containing 100 μM diisopropyl fluorophosphate. After 2

minutes at 4°C, membranes (approximately 0.5 mg) were incubated with 3 nM [3H]-(–)-nicotine, test drug, 1 μM atropine, and either 2 mM $CaCl_2$ or 0.5 mM EGTA for 1 hour at 4°C, and then filtered over Whatman glass fibre filters (thickness C) (pretreated for 1 hour with 0.5% PEI) using a Brandel cell harvester. Nonspecific binding was described by 100 μM carbachol, and specific binding was typically 84%.

Binding data analysis for Tests A and B

IC_{50} values and pseudo Hill coefficients (n_H) were calculated using the non-linear curve fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding K_D values of 1.67 and 1.70 nM for the ^{125}I-α-BTX and [^{3}H]-(–)-nicotine ligands respectively. K_i values were estimated using the general Cheng-Prusoff equation:

$$K_i = [IC_{50}]/((2+([ligand]/[K_D])^n)^{1/n} - 1)$$

where a value of n=1 was used whenever $n_H<1.5$ and a value of n=2 was used when $n_H \geq 1.5$. Samples were assayed in triplicate and were typically ±5%. K_i values were determined using 6 or more drug concentrations. The compounds of the invention are compounds with binding affinities (K_i) of less than 1000 nM in either Test A or Test B, indicating that they are expected to have useful therapeutic activity.

EXAMPLES

Commercial reagents were used without further purification. Mass spectra were recorded using either a Hewlett Packard 5988A or a FisonsMass Quattro-1 Mass Spectrometer and are reported as m/z for the parent molecular ion with its relative intensity. Room temperature refers to 20–25°C.

The following examples are preferred non-limiting examples embodying preferred aspects of the invention.

Preparation 1

Spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] N-borane complex (compound III)

A mixture of trimethylsulfoxonium iodide (16.10 g, 73.2 mmol) and a dispersion of sodium hydride (60% in oil, 3.00 g, 75.0 mmol) in anhydrous dimethyl sulfoxide was stirred at room temperature under nitrogen for 30 minutes. Quinuclidin-3-one (II) (7.05 g, 56.3 mmol) was then added as a solid portionwise, and the resulting mixture was stirred at 65–70°C under nitrogen for 1 hour. The reaction mixture was cooled, water was added (200 ml), and the resulting solution was extracted with chloroform (3 x 200 ml). The chloroform extracts were combined, and back-extracted with water (4 x 200 ml). The chloroform layer was then dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] (6.51 g, 46.8 mmol, 83%) as a clear, colorless liquid. To a stirred solution of spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] (5.3 g, 38.1 mmol) in anhydrous tetrahydrofuran (100 ml) at 0°C was added dropwise a solution of borane in tetrahydrofuran (1.0 M, 38.1 ml, 38.1 mmol), and resulting solution was stirred at 0°C under nitrogen for 30 minutes. Brine (100 ml) was added cautiously to the reaction solution, and the resulting aqueous mixture was extracted with ethyl acetate (2 x 100 ml). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the title compound (III) (4.3 g, 28.1 mmol, 74%) as a white solid: electrospray MS 152 ($[M-H]^+$, 15).

Preparation 2

3-(2-Chloropyridin-3-ylmethyl) -oxy-1-azabicyclo[2.2.2]oc -borane complex (compound IV)

A solution of phenyllithium (1. cyclohexane/ether [7:3], 1 .3 mol, 3 eq.) was ded via a cannula to anhydr hydrofuran (350 ml) at –6 r a nitrogen nosphere. Then, diisopropyl .7 ml, 5mmol) was adde e, followed by a opwise addition of 2-chloro 28.4 ml, 0.3 mol, 3 eq.) inutes. The ulting solution was stirred nder nitrogen for 1.5 h olution was then

cooled to –60°C, and a solution of spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] N-borane complex (15.3 g, 0.1 mol) in tetrahydrofuran (75 ml) was added dropwise. The resulting reaction mixture was then stirred at –40°C under nitrogen. After 3 hours, a saturated solution of sodium bicarbonate (150 ml) was slowly added, followed by water (400 ml), and the resulting aqueous mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 100 ml). The organic layers were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Column chromatography using silica gel and elution with ethyl acetate/hexanes [3:2] afforded the title compound IV as a tan solid (17.5 g, 65.6 mmol, 66%): electrospray MS 269 ($[MH]^+$ with ^{37}Cl, 10), 267 ($[MH]^+$ with ^{35}Cl, 26).

Preparation 3

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (compound V)

3-(2-Chloropyridin-3-ylmethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane N-borane complex (17.4 g, 65.3 mmol) was dissolved in anhydrous N,N-dimethylformamide (500 ml), the resulting solution was cooled to 0°C under nitrogen, and a dispersion of sodium hydride (60% in oil, 6.55 g, 163 mmol, 2.5 eq.) was added portionwise. The resulting solution was stirred at room temperature under nitrogen for 16 hours. A saturated solution of ammonium chloride (50 ml) was then added at 0°C, followed by ice water (500 ml), and the resulting aqueous mixture was extracted with chloroform (4 x 125 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford an orange solid. Purification through a short column of silica gel eluting with chloroform/acetone [95:5 to 85:15], follow[illegible]by stirring in hexanes (100ml) and filtration, provided a yellow solid (12.7 g, 55.2 mm[illegible]%) of spiro[1-azabicyclo[2.2.0]octane-3,2'(3'H)-furo[2,3-b]pyridine] N-borane [illegible]x, electrospray MS 231 ($[MH]^+$, 65).

Spiro[1-azabicyclo[2[illegible]ne-3,2'(3'H)-furo[2,3-b]pyridine] N-borane complex (12.2 g, 53 mmol) was disso[illegible]0 ml of acetone, the solutio[illegible]s cooled to 0°C, and an aqueous solution of [illegible]; 50 mL) was added. The r[illegible]ng solution was stirred at room temperature u[illegible]en for 24 hours. The reacti[illegible]as concentrated under reduced pressure, ar[illegible]ous residue was treated w[illegible]rated aqueous sodium carbonate solution ([illegible] solution was basified to [illegible] using solid sodium

carbonate, and the resulting solution was extracted with chloroform (3 x 100 ml). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the title compound VI (11.2 g, 51.8 mmol, 98%, 54% overall) as an off-white solid: electrospray MS 217 ($[MH]^+$, 72).

The title compound was separated into its (R)- and (S)-enantiomers by either of the following methods:

Method A - 250 mg of the title compound was separated by chiral HPLC, using a 2cm X 25cm CHIRALCEL-OD column on a Waters Delta Prep 3000 Preparative Chromatography System, eluting with 2,2,4-trimethylpentane/ethanol (92:8 to 9:1) at a flow rate of 20 ml/min. This provided 111 mg of the (S)-enantiomer ($[\alpha]^{23} = +59.7$ (c = 1, methanol)) and 90 mg of the (R)-enantiomer ($[\alpha]^{23} = -63.9$ (c = 1, methanol)).

Method B - 1 g (4.62 mmol) of the title compound was treated with L-(+)-tartaric acid (694 mg; 4.62 mmol) in 15 % aqueous ethanol (10 ml) and recrystallized three times to obtain the (S)-enantiomer L-(+)-tartrate (650 mg; 1.77 mmol; $[\alpha]^{23} = +57.7$ (c = 2, H_2O)). The filtrates were concentrated under reduced pressure and the aqueous residue was basified to pH >10 using solid sodium carbonate. The resulting mixture was extracted with chloroform (3 x 25 ml) and the combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure. The residue (650 mg; 3 mmol) was treated with D-(–)-tartaric acid (452 mg; 3 mmol) and recrystallized as above to provide the (R)-enantiomer D-(–)-tartrate (775 mg; 2.11 mmol; $[\alpha]^{23} = -58.2°$ (c = 2, H_2O)).

Preparation 4

(R)-(–)-5'-Nitrospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (compound VI, E=NO_2)

(R)-(–)-Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (3.03 g, 14 mmol) was dissolved in concentrated sulfuric acid (7 ml) at 0 °C, fuming nitric acid (3.3 g, 70.2 mmol) was added over 10 minutes, the mixture was stirred for 1 hour, and heated at 65 – 70°C for 24 hours, cooled, poured onto ice (20 g), added 300 ml of water, basified to pH 10 with solid potassium carbonate, stirred for 1 h, filtered off and dried, providing the solid title compound (3.6 g, 13.8 mmol, 98%): electrospray MS 262 ($[MH]^+$, 10

Preparation 5

(R)-(–)- 5'-Aminospiro[1-azabicyclo-[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (compound VI, E=NH_2)

A mixture of the enantiomer (R)-(–)-5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (3.8 g, 13.3 mmol) and 10% palladium on carbon (48% water wet, 270 g) in methanol (90 ml) was hydrogenated for 1 hour at 50 psi of hydrogen. The catalyst was filtered off through a pad of celite and the solvent was evaporated under reduced pressure; the residue was purified by flash chromatography (eluting with ammoniated chloroform/methanol, 95:5 to 85:15), provided the title compound (2.5 g, 10.8 mmol, 81%): electrospray MS (m/z, relative intensity) 232 ($[MH]^+$, 100).

Preparation 6

(R)-(–)-Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-N-oxide] (compound VII)

A solution of 2.03 g (9.38 mmol) of (R)-(–)-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] in 100 ml of methylene chloride was cooled in an ice bath, to which was added 6.90 g (22.8 mmol) of 57-86% m-chloroperbenzoic acid, in portions over 5 minutes. The reaction was allowed to warm gradually to ambient temperature and stirred for 24 hours total. The solvent was removed *in vacuo* and the solid residue was dissolved in 100 ml of absolute ethanol, cooled in an ice bath, and sulfur dioxide was bubbled in until the solution turned cloudy. The reaction was stirred for 4 hours, then the solvent was removed *in vacuo*. The solid residue was dissolved in 150 ml of a 9:1 mixture of chloroform and methanol, then extracted with 50 ml of 10% aqueous sodium hydroxide. The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and flash chromatographed through neutral silica gel using a 9:1 mixture of chloroform and 2.0 M ammonia in methanol as the eluant, giving 1.30 g (60%) of the title compound following crystallization from ethyl acetate/hexane (1:1): $[\alpha]^{23} = -56.82$ (c = 1.09, EtOH), electrospray MS 233 ($[MH]^+$, 100).

Preparation 7A

5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (compound VI, E = Br)

A solution of spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (100 mg, 0.462 mmol) and sodium acetate (410 mg, 5 mmol) in 50 % aqueous acetic acid (4ml) was heated to 60°C. Bromine (0.100 ml, 1.94 mmol) was added via a syringe over 10 minutes, the solution was then heated [illegible] reflux for 1 hour. The mixture was allowed to cool [illegible] ambient temperature, basified [illegible] >10 with sodium carbonate, and extracted with [illegible] chloroform (3 x 15 ml). The co[illegible] extracts were dried ($MgSO_4$), filtered, and [illegible] trated under reduced press[illegible] ve the title compound (110 mg, 0.37 mmol, 81 %) [illegible] off-white solid: electrospr[illegible] 95 ($[MH]^+$, with ^{79}Br, 100) [illegible] 7 ($[MH]^+$, with [illegible] 8).

Preparation 7B

(R)-(–)- 5'-Bromospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (compound VI, E = Br)

The enantiomer (R)-(–)- spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] (1.95 g, 9 mmol) treated in the same way as described in preparation 7A provided the title compound (1.77 g, 6 mmol, 67%) ($[\alpha]^{23} = -45.5\,^{\circ}$ (c = 1, MeOH)).

Example 1

R-(–)-5'-N-(Phenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

Sodium spheres were blotted dry of mineral spirits, weighed (100 mg, 4.3 mmol) and added gradually to 2 ml of anhydrous methanol, while stirring under a nitrogen atmosphere at 0°C. The reaction was stirred at 0°C for 25 minutes, during which time the vigorous bubbling stopped and nearly all the solid dissolved. 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] (230 mg, 1.0 mmol) and benzaldehyde (0.23 ml, 1.0 mmol) were added, the ice bath was removed, and an additional 2 ml of anhydrous methanol was added. The solution was stirred at room temperature for two days, then heated to 50°C for 2 hrs. Sodium borohydride (106mg , 2.8 mmol) was added and the reaction was heated at reflux for 90 minutes. Upon cooling to ambient temperature, the methanol was removed *in vacuo* and the residue was partitioned between 8 ml of chloroform and 2ml of water. The aqueous layer was extracted two more times with 8 ml of chloroform and the organic layers were combined and dried over magnesium sulfate. The chloroform was stripped *in vacuo*, and the crude product was purified on a silica flash column using a 0-10% ammoniated methanol/chloroform gradient, giving 0.25g (77%) of the title compound as a white powder: electrospray MS 322 $[MH]^+$, 100).

Example 2

(–)-5'-N-(2-Pyridylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 115 mg (0.5 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 0.114 ml (1.2 mmol) of 2-pyridine carboxaldehyde to give 84 mg of the title compound as a beige powder (52%.): electrospray MS 323 ([MH]$^+$, 100).

Example 3

R-(–)-5'-N-(3-Pyridylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 115 mg (0.5 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 3-pyridinecarboxaldehyde to give 81 mg, (50%) of the title compound as a beige powder: electrospray MS 323 ([MH]$^+$, 100).

Example 4

R-(–)-5'-N-(4-Pyridylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 115 mg (0.5 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 4-pyridinecarboxaldehyde to give 84 mg, (52%) of the title compound as a light yellow powder: electrospray MS 323 ([MH]$^+$, 100).

Example 5

R-(–)-5'-N-(2-Furanylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 2-furaldehyde (50 µl, 0.52 mmol), giving 30 mg of the title compound as a dark yellow semi-solid: electrospray MS 312 ([MH]$^+$, 100).

Example 6

R-(–)-5'-N-(3-Furanylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3.2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 3-furaldehyde to give 25 mg of the title compound: electrospray MS 312 ($[MH]^+$, 100).

Example 7

R-(–)-5'-N-(2-Thienylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 2-thiophenecarboxaldehyde, giving 9 mg of the title compound: electrospray MS 328 ($[MH]^+$, 100).

Example 8

R-(–)-5'-N-(4-Methoxyphenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 4-methoxybenzaldehyde, providing 18 mg of the title compound: electrospray MS 352 ($[MH]^+$, 100).

Example 9

R-(–)-5'-N-(4-Chlorophenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 4-chlorobenzaldehyde to give 62 mg of the title compound: electrospray MS 356 $[MH]^+$, ^{37}C

Example 10

R-(–)-5'-N-(4-Methylphenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 4-tolualdehyde, giving 6 mg of the title compound: electrospray MS 336 ([MH]$^+$, 100).

Example 11

R-(–)-5'-N-(3,4-Dichlorophenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 3,4-dichlorobenzaldehyde to give 19 mg of the title compound: electrospray MS 390 [MH]$^+$, $^{37}Cl_1$ 392, $^{37}Cl_2$ 394.

Example 12

R-(–)-5'-N-(2-Imidazolylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 2-imidazolecarboxaldehyde, giving 57 mg of the title compound: electrospray MS 312 ([MH]$^+$, 100).

Example 13

R-(–)-5'-N-Acetyl-N-(phenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

Acetic anhydride (25 µl, 0.26 mmol) was added to a solution of R-(–)-5'-N-(phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] (50 mg, 0.15 mmol) in 1 ml of anhydrous pyridine under nitrogen. The reaction was heated at 95°C in an oil bath, then cooled to ambient temperature and poured into cooled

sodium carbonate. The product was extracted with four portions of chloroform. The organic layers were combined, dried over magnesium sulfate, and stripped *in vacuo*. The crude product was passed through a Supelco Visiprep using chloroform and then a 5-15% ammoniated methanol/chloroform gradient. The solvents were removed *in vacuo*, and the purified product was dissolved in methanol and acidified with 0.9 ml of 1.0 M hydrogen chlroride in ether.to provide 59 mg (61%) of the title compound as a white semi-solid: electrospray MS 364 ([MH]$^+$, 100).

Example 14

R-(–)-5'-N-Methyl-N-(phenylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

Under a nitrogen atmosphere, sodium cyanoborohydride (39 mg, 0.62 mmol) was added to a solution of 50 mg, (0.22 mmol) of R-(–)-5'-N-(phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 165 µl (2.2 mmol) of 37% aqueous formaldehyde in 1 ml of deionized water adjusted to pH 3 using concentrated hydrochloric acid. The reaction was stirred at room temperature, adding acid to adjust the pH whenever it rose above 6. After one hour, the reaction was poured into saturated sodium carbonate and this was extracted with four portions of chloroform. The organic layers were combined, dried over magnesium sulfate, and stripped *in vacuo*. The residue was passed through a Supelco Visiprep using an ammoniated methanol/chloroform gradient. The solvents were removed *in vacuo*, and residue wa[illegible]n up in methanol and acidified with 0.9 ml of 1.0 M hydrogen chloride in ether. Rem[illegible]of the solvent *in vacuo* gave 64 mg (98%) of the HCl salt of the title compound as a l[illegible]low semi-solid: electrospray MS 336 ([MH]$^+$, 100).

Example 15

(R)-(–)-5'-N-(3-Pyridylamin[illegible]o[1-azabicyclo[2.2.2]octar[illegible])-furo[2,3-b]pyridine]

In a pressure tube sealed und[illegible]rogen, (R)-(–)-5'-bromosp[illegible]cyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridin[illegible]5.1 mg, 0.36 mmol), 3-am[illegible](69 mg, 0.73

mmol), tris(dibenzylidineacetone)dipalladium (0) (21 mg, 0.023 mmol), racemic-2-2'-bis(diphenylphosphino)1,1'-binaphthyl (34mg, 0.055 mmol), sodium t-butoxide (0.105 g, 1.09 mmol), and 1,2-dimethoxyethane (5 ml) were heated and stirred at 100°C. After 3 days the solution was allowed to cool, and partitioned between water and chloroform. The chloroform layer was then dried by addition of magnesium sulfate and filtered through a solid phase extraction cartridge containing 5 g silica. The crude product was eluted from the cartridge with a 1:1 v/v mixture of methanolic ammonia and chloroform; the resulting solution was evaporated. The residue was purified by reverse phase HPLC on a C-18 column using a gradient of 0-50% acetonitrile and 0.1% aqueous trifluoroacetic acid as the eluant. The product-containing fractions were evaporated and the product was dissolved in a small volume of methanol (ca. 5 ml), and excess hydrogen chloride (1 M solution in ether, appr. 5 ml) was added. The solution was re-evaporated to give the title compound (54 mg, 0.13 mmol) as a hydrochloride salt: electrospray MS 309 ([MH]$^+$, 100); $[\alpha]_{589nm}$ = -42.0 (c = 0.1, MeOH).

Example 16

R-(–)-6'-N-(Phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

(R)-(–)-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-N-oxide] (VII) [970 mg (4.20 mmol)] was dissolved in 10 ml of phosphorus oxychloride, while stirring in an ice bath. The suspension was then heated to reflux and stirred for 5 hours. Upon cooling to ambient temperature, the reaction was poured onto 100 g of ice, diluted with 100 ml of water, made basic with potassium carbonate, and extracted with chloroform (3 x 50 ml). The combined organic extract was dried over anhydrous magnesium sulfate, concentrated in vacuo, and flash chromatographed through neutral silica gel using a 95:5 mixture of chloroform and 2.0N ammonia in methanol to give 700 (R)-(–)-6-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] as a white solid.

A solution of 85 mg (0.34 mmol) of the chloride in 3.0 benzylamine was heated to reflux, under a nitrogen atmosphere, for 23 hours. Upon cooling to ambient temperature,

the solution was flash chromatographed through neutral silica gel using a 9:1 mixture of chloroform and 2.0N ammonia in methanol, providing 22 mg (20%) of the title compound, electrospray MS 322 ([MH]$^+$, 100).

Example 17

R-(–)-5'-N-(3-Thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 3-thiophenecarboxaldehyde, giving 61 mg (85%) of the title compound: electrospray MS 328 ([MH]$^+$, 100).

Example 18

R-(–)-5'-N-(2-Phenylethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and phenylacetaldehyde, giving 31 mg of the title compound: electrospray MS 336 ([MH]$^+$, 100).

Example 19

R-(–)-5'-N-(3-Phenylpropyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 3-phenylpropionaldehyde, giving 42 mg of the title compound: electrospray MS ([MH]$^+$, 100).

Example 20

R-(–)-5'-N-(Quinolin-3-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 3-quinolinecarboxaldehyde, giving 47 mg of the title compound: electrospray MS 373 ([MH]$^+$, 100).

Example 21

R-(–)-5'-N-(Quinolin-4-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 4-quinolinecarboxaldehyde, giving 3 mg of the title compound: electrospray MS 373 ([MH]$^+$, 100).

Example 22

R-(–)-5'-N-(1,4-Benzodioxan-6-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 1,4-benzodioxan-6-ylcarboxaldehyde, giving 31 mg of the title compound: electrospray MS 380 ([MH]$^+$, 100).

Example 23

R-(–)-5'-N-(Imidazol-4-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from [illegible] mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 4(5)-imidazolecarboxaldehyde, giving [illegible] mg of the title compound: electrospray MS 312 ([MH]$^+$, 100).

Example 24

R-(–)-5'-N-(*trans*-3-pyridinylprop-2-enyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and cinnamaldehyde, giving 43 mg of the title compound: electrospray MS 348 ([MH]$^+$, 100).

Example 25

R-(–)-5'-N-(Thiazol-2-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 1 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 2-thiazolecarboxaldehyde, giving 13 mg of the title compound: electrospray MS 329 ([MH]$^+$, 100).

Example 26

R-(–)-5'-N-(3-Methylphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

Titanium tetrachloride (0.5 ml of a 1.0 M solution in dichloromethane) was added to a solution of 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine], 0.066 ml (0.47 mmol) of triethylamine and 0.026 ml (0.22 mmol) of m-tolualdehyde in 2 ml of chloroform, under a nitrogen atmosphere. After stirring for 16 h, a solution of 0.65 [illegible] of sodium cyanoborohydride in 0.55 ml of methanol was added; the resulting [illegible] was stirred for 20 min, then poured into 20 ml [illegible]eous sodium carbonate and [illegible]d with chloroform (4 x 10 [illegible]. The combined [illegible]c extract was dried over ma[illegible] sulfate, concentrated in va[illegible]uo and flash [illegible]atographed through neutral [illegible] using a 0-15% ammoniat[illegible]anol/chloroform gradient, gi[illegible]g (81%) of the title comp[illegible] electrospray MS [illegible]MH]$^+$, 100).

Example 27

R-(–)-5'-N-(2-Chlorophenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 26 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 2-chlorobenzaldehyde, giving 63 mg of the title compound: electrospray MS 356 ([MH]$^+$, 100).

Example 28

R-(–)-5'-N-(3-Chlorophenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 26 from 50 mg (0.22 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 2-chlorobenzaldehyde, giving 50 mg of the title compound: electrospray MS 356 ([MH]$^+$, 100).

Example 29

R-(–)-5'-N-(3-Phenylpropynyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 26 from 400 mg (1.76 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 3-phenylpropargyl aldehyde, giving 212 mg of the title compound: electrospray MS 346 ([MH]$^+$, 100).

Example 30

R-(–)-5'-N-(3-Hydroxyphen yl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was pr y the procedure used in Exa 26 from 250 mg (1.10 mol) of R-(–)-5'-amino abicyclo[2.2.2]octane-3,2'-( )-furo[2,3-b]pyridine] d 3-hydroxybenzaldehyd 117 mg of the title compou lectrospray MS 338 H]$^+$, 100).

Example 31

R-(–)-5'-N-(4-Hydroxyphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 26 from 250 mg (1.10 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 4-hydroxybenzaldehyde, giving 31 mg of the title compound: electrospray MS 338 ([MH]$^+$, 100).

Example 32

R-(–)-5'-N-[*trans*-3-(4-Pyridinyl)prop-2-enyl]aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 26 from 250 mg (1.10 mmol) of R-(–)-5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and *trans*-3-pyridylpropenal, giving 77 mg of the title compound: electrospray MS 349 ([MH]$^+$, 100).

Example 33

R-(–)-5'-N-Acetyl-N-(3-thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 13 from 100 mg of R-(–)-5'-N-(3-thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and acetic anhydride, giving 25 mg of the title compound: electrospray MS 370 ([MH]$^+$, 100).

Example 34

R-(–)-5'-N-Methyl-N-(4-pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 14 from 100 mg of (–)-5'-N-(4-pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-

b]pyridine] and 37% aqueous formaldehyde, giving 26 mg of the title compound: electrospray MS 337 ([MH]$^+$, 100).

Example 35

R-(–)-5'-N-Methyl-N-(3-pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 14 from 200 mg of R-(–)-5'-N-(3-pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and 37% aqueous formaldehyde, giving 190 mg of the title compound: electrospray MS 337 ([MH]$^+$, 100).

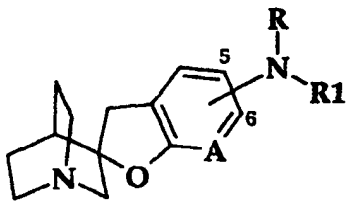
Example 36

R-(–)-5'-N-(2-Hydroxyethyl)-N-(3-thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]

The title compound was prepared by the procedure used in Example 14 from 100 mg of R-(–)-5'-N-(3-thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and glyoxal, giving 54 mg of the title compound: electrospray MS 372 ([MH]$^+$, 100).

CLAIMS

1. A compound of formula I,



I

wherein

NRR_1 is attached at the 5- or 6-position of the furopyridine ring;

R is hydrogen, C_1-C_4 alkyl, or COR_2;

R_1 is $(CH_2)_nAr$, $CH_2CH{=}CHAr$, or $CH_2C{\equiv}CAr$;

n is 0 to 3;

A is N or NO;

Ar is a 5- or 6-membered aromatic or heteroaromatic ring which contains zero to four nitrogen atoms, zero to one oxygen atoms, and zero to one sulfur atoms;

or: an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing zero to four nitrogen atoms, zero to one oxygen atoms, and zero to one sulfur atoms; any of which may optionally be substituted with one to two substitutents independently selected from: halogen, trifluoromethyl, or C_1-C_4 alkyl;

hydrogen, C_1-C_4 alkyl; C_1-C_4 alkoxy; or phenyl ring optionally substituted with o three of the following su ents: halogen, C_1–C_4 alkyl, C_2-C_4 alkenyl, C_2–kynyl, OH, OC_1–C_4 alkyl, -R_5, –CN, $–NO_2$, $–NR_3R_4$, or $–CF_3$;

R_3, R_4 and R_5 are independently hydrogen; C_1-C_4 alkyl; or phenyl ring optionally substituted with one to three of the following substituents: halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH, OC_1–C_4 alkyl,–CN; $–NO_2$, or $–CF_3$;
or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein A is N; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1 or 2, wherein R_1 is $(CH_2)_nAr$; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

4. A compound according to claim 1 or 2, wherein R_1 is $CH_2CH=CHAr$; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

5. A compound according to claim 1 or 2, wherein R_1 is $CH_2C\equiv CAr$; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

6. A compound according to any one of claims 1 to 5, wherein Ar is selected from the group: phenyl ring optionally substituted with one to three of the following substituents: halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, OH, OC_1–C_4 alkyl, CO_2R_5, –CN, $–NO_2$, $–NR_3R_4$, and $–CF_3$; 2-, 3-, or 4-pyridyl; 2-, or 3-furanyl; 2-, or 3-thienyl; 2-, or 4-imidazolyl; 1, 2-, or 3-pyrrolyl; 2-, or 4-oxazolyl; and 3-, or 4-isoxazolyl;
or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

A compound according to any one of claims 1 to 5, wherein Ar is selected from the group: 1-, or 2-naphthyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl; 2-, 4-, 5-, 6-, or 7-benzoxazolyl; and 3-, 4-, 5-, 6-, or 7-benzisoxazolyl; or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

8. A compound according to any one of claims 1 to 6, wherein R_3, R_4 and R_5 are independently hydrogen, or C_1-C_4 alkyl;
or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

9. A compound according to any one of claims 1 to 8, wherein n is 1.

10. A compound according to any one of claims 1 to 8, wherein R is hydrogen.

11. A compound according to any one of claims 1 to 8, wherein Ar is an heteroaromatic ring.

12. A compound according to any one of claims 1 to 8 wherein n is 1; R is hydrogen and Ar is an heteroaromatic ring.

13. A compound according to claim 1, said compound being:
R-(–)-5'-N-(Phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
R-(–)-5'-(2-Pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
R-(–)-5'-(3-Pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
R-(–)-5'-(4-Pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
R-(–)-5'-(2-Furylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
R-(–)-5'-(3-Furylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
R-(–)-5'-(2-Thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
R-(–)-5'-(2-Imidazolylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(4-Methoxyphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(4-Chlorophenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(4-Methylphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3,4-Dichlorophenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Acetyl- N-(phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Methyl-N-(phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

(R)-(–)-5'-N-(3-Pyridyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];

(R)-(–)-6'-N-(Phenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(2-Phenylethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Phenylpropyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(Quinolin-3-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(Quinolin-4-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(1,4-Benzodioxan-6-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(Imidazol-4-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(*trans*-3-Phenylprop-2-enyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(Thiazol-2-ylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Methylphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(2-Chlorophenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Chlorophenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Phenylpropynyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(3-Hydroxyphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(4-Hydroxyphenylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-[*trans*-3-(4-Pyridinyl)prop-2-enyl]aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Acetyl-N-(3-thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Methyl-N-(4-pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-Methyl-N-(3-pyridylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

R-(–)-5'-N-(2-Hydroxyethyl)-N-(3-thienylmethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

an enantiomer thereof, and pharmaceutically acceptable salts th

14 ompound according to claim aid compound being:

-)-5'-(3-Pyridylmethyl) ami o[1-azabicyclo[2.2.2]octan H)-[2,3-b]pyridine];

R-(–)-5'-(4-Pyridylmethyl) aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
or an enantiomer thereof, and pharmaceutically acceptable salts thereof.

15. A compound according to any one of claims 1 to 14 for use in therapy.

16. A pharmaceutical composition including a compound as defined in any one of claims 1 to 14, in admixture with an inert pharmaceutically acceptable diluent or carrier.

17. The pharmaceutical composition according to claim 16, for use in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

18. The pharmaceutical composition according to claim 16, for use in the treatment or prophylaxis of human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial.

19. The pharmaceutical composition according to claim 16, for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

20. The pharmaceutical composition according to claim 19, for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, Lewy Body Dementia, memory loss or Attention Deficit Hyperactivity Disorder.

21. The pharmaceutical composition according to claim 19, for use in the treatment or prophylaxis of anxiety, schizophrenia, mania or manic depression.

22. The pharmaceutical composition according to claim 19, for use in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

23. The pharmaceutical composition according to claim 19, for use in the treatment or prophylaxis of jetlag, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

24. The pharmaceutical composition according to claim 19, for use in the treatment or prophylaxis of Alzheimer's disease.

25. Use of a compound as defined in any one of claims 1 to 14, in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

26. The use of a compound as defined in any one of claims 1 to 14, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial.

27. The use according to claim 25 or claim 26, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapses, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

28. The use according to claim 27, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, Lewy Body Dementia, memory loss or Attention Deficit Hyperactivity Disorder.

29. The use according to claim 27, wherein the condition or disorder is anxiety, schizophrenia, mania or manic depression.

30. The use according to claim 27, wherein the condition or disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

31. The use according to claim 27, wherein the condition or disorder is jetlag, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

32. The use according to claim 27, wherein the condition or disorder is Alzheimer's disease.

33. A method of treatment or prophylaxis of psychotic disorders or intellectual impairment disorders, which comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 14.

34. A method of treatment or prophylaxis of human diseases or conditions in which activation of the α7 nicotinic receptor is beneficial, which comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 14.

35. The method according to claim 33 or claim 34, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, Lewy Body Dementia, anxiety, schizophrenia, mania or manic depression, Parkinson's disease, Huntington

disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

36. The method according to claim 33 or claim 34, wherein the condition or disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, Lewy Body Dementia, memory loss or Attention Deficit Hyperactivity Disorder.

37. The method according to claim 33 or claim 34, wherein the condition or disorder is anxiety, schizophrenia, mania or manic depression.

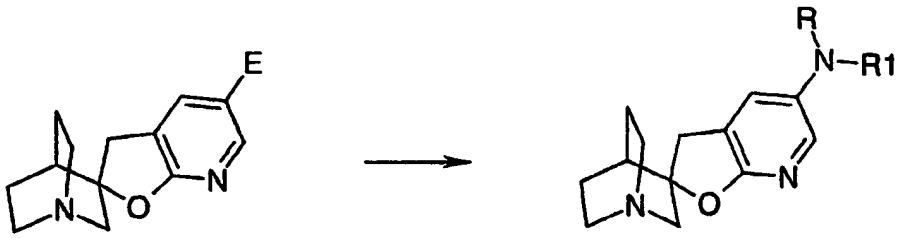
38. The method according to claim 33 or claim 34, wherein the condition or disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

39. The method according to claim 33 or claim 34, wherein the condition or disorder is jetlag, nicotine addiction including that resulting from exposure to products containing nicotine, pain, or ulcerative colitis.

40. The method according to claim 33 or claim 34, wherein the condition or disorder is Alzheimer's disease.

41. A process for preparing a compound of formula I, as defined in any one of claims 1 to 14, or an enantiomer thereof, and pharmaceutically acceptable salts thereof, which comprises

(a) for preparing compounds where R1 is positioned in the 5'-p
alating or acylating compound nula VI, wherein E is halo $_2$, or
, in a suitable solvent:



VI VIII (I)

or b) for preparing compounds wherein NRR1 is positioned in the 5'-position, reacting compounds of formula VI, wherein E is halogen, NO_2, or NHR, with an amine in the presence of a suitable organometallic catalyst, base and solvent:

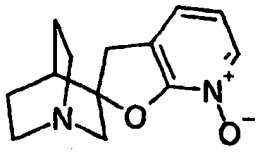
VI VIII (I)

or c) for preparing compounds wherein NRR1 is positioned in the 6'-position, reacting compounds of formula VII, with a halogenating reagent, followed by reaction with an amine in an inert solvent:

VII IX ()

d) for preparing compou in NRR1 is positioned in t 6'-position, idising compounds of fo or IX with a peroxidic rea in a suitable vent, followed by partia

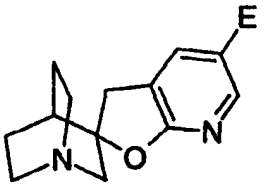
42. A compound of the formula



VII

5

43. A compound of the formula



VI

where E is NO_2, NHR, or halogen.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02478

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 491/22, A61K 31/439, A61P 25/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9903859 A1 (ASTRA AKTIEBOLAG), 28 January 1999 (28.01.99) --	1-43
A	WO 9705139 A1 (ABBOTT LABORATORIES), 13 February 1997 (13.02.97), see claims 1, 3 --	1-43
A	WO 9606098 A1 (ASTRA AKATIEBOLAG), 29 February 1996 (29.02.96), see abstract --	1-43
A	EP 0311313 A2 (YAMANOUCHI PHARMACEUTICAL CO. LTD.), 12 April 1989 (12.04.89), see claim 1 --	1-43

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2000	16 -05- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebojsa Ö Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02478

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9741125 A1 (SMITHKLINE BEECHAM PLC), 6 November 1997 (06.11.97), see claim 7	1-43

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/02478

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 33-40
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ ed additional search fees were timely paid by the applicant. Consequently, this international search report is o the invention first mentioned in the claims; it is covered by claims Nos.:

Remark

☐ The additional search fees were accompanied by the applicant's

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02478

Claims 33-40 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (see PCT, Rule 39.1 (iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/02478

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9903859 A1	28/01/99	AU 8367998 A	10/02/99
		SE 9702746 D	00/00/00
		SE 9800977 D	00/00/00
WO 9705139 A1	13/02/97	CA 2227695 A	13/02/97
		EP 0842178 A	20/05/98
		JP 11510171 T	07/09/99
WO 9606098 A1	29/02/96	AU 690735 B	30/04/98
		AU 3401895 A	14/03/96
		BR 9508751 A	12/08/97
		CN 1159808 A	17/09/97
		CZ 9700392 A	17/12/97
		EP 0777671 A	11/06/97
		FI 970762 A	24/02/97
		GB 9417084 D	00/00/00
		HU 77352 A	30/03/98
		IL 115039 D	00/00/00
		JP 10504561 T	06/05/98
		NZ 292289 A	27/05/98
		PL 318760 A	07/07/97
		SK 21697 A	10/09/97
		TR 960167 A	00/00/00
		US 5902814 A	11/05/99
		ZA 9507122 A	18/04/96
		GB 9504627 D	00/00/00
		NO 970800 A	21/02/97
EP 0311313 A2	12/04/89	SE 0311313 T3	
		AT 122353 T	15/05/95
		AU 621559 B	19/03/92
		CA 1337817 A	26/12/95
		CN 1033629 A	05/07/89
		CN 1036653 B	10/12/97
		DE 3853758 D,T	07/09/95
		DK 554288 A	26/05/89
		ES 2074[illegible]41 T	16/09/95
		GR 3016[illegible]95 T	30/11/95
		HU 21[illegible]87 B	28/12/95
		HU 950[illegible]33 A	28/11/95
		KR 970[illegible]7 B	19/05/97
		NO 88[illegible] A	06/04/89
		US RE[illegible] E	05/07/94
		US 49[illegible] A	10/07/90
		US 49[illegible] A	26/02/91
		US 50[illegible] A	20/08/91
		US 54[illegible]	02/05/95
		JP 19[illegible]	18/09/95
		JP 2[illegible]	06/02/90
		MX 9[illegible]	31/07/92

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/02478

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9741125 A1	06/11/97	EP 0900221 A	10/03/99
		GB 9608850 D	00/00/00
		GB 9608828 D	00/00/00
		GB 9608851 D	00/00/00
		GB 9608852 D	00/00/00

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ENT COOPERATION TREATY

PCT

REC'D 11 JUN 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference J 2090-1 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE 99/02478	International filing date *(day/month/year)* 23.12.1999	Priority date *(day/month/year)* 15.01.1999
International Patent Classification (IPC) or national classification and IPC7 C 07 D 491/22, A 61 K 31/439, A 61 P 25/00		
Applicant ASTRAZENECA ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.07.2000	14.05.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Nebil Gecer/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE 99/02478

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement) under article 19

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/02478

III. Non-establishment of opinion with regard t novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 33-40

because:

☒ the said international application, or the said claims Nos. 33-40
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/02478

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step r industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-32, 41-43	YES
	Claims		NO
Inventive step (IS)	Claims	1-32, 41-43	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-32, 41-43	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The claimed invention relates to substituted amines of spirofuropyridines, to pharmaceutical compositions containing them and to the use of the compounds in therapy. Also claimed is a process for preparing the compounds and certain intermediates.
The compounds are potent ligands for nicotinic acetylcholine receptors (nAChR´s).

The following relevant documents are cited in the international search report:

D1) WO 9705139 A1
D2) WO 9606098 A1
D3) EP 311313 A2
D4) WO 9741125 A1

D1 relates to furopyridine, thienopyridine, pyrrolopyridine and related pyrimidine, pyridazine and triazine compounds which are selective and potent cholinergic compounds useful in controlling synaptic transmission.

D2 relates to spiro-azabicyclic compounds which are useful in the treatment of psychotic disorders, intellectual impairment disorders and anxiety.

D3 relates to heterocyclic spiro compounds which are particularly useful for the prevention and treatment of diseases caused by nervous degeneration.

D4 relates to spiroazabicyclic compounds which are useful in the treatment of CNS disorders.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

None of D1-D4 discloses compounds which are included in the claimed scope or closely related compounds. D1-D4 only disclose the general state of the art, which is not considered to be of particular relevance

Claims 33-40 relate to the treatment of diseases. Claims of this kind may be accepted and examined in some countries. However, owing to the difference in national practice and laws, it is not possible for the International Preliminary Examining Authority to give a statement on such claims that would be equally valid for all states. The consideration thereafter given, must therefore be based on the acceptance of such claims according to national legislation.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE99/02478

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 9903859	28.01.1999	10.07.1998	18.07.1997

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

09/529654

5020

09529654

VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS

PCT

INTERNATIONALER VORLÄUFIGER PRÜFUNGSBERICHT

16 T

(Artikel 36 und Regel 70 PCT)

Aktenzeichen des Anmelders oder Anwalts	WEITERES VORGEHEN	siehe Mitteilung über die Übersendung des internationalen vorläufigen Prüfungsbericht (Formblatt PCT/IPEA/416)
195-2 PCT		
Internationales Aktenzeichen	Internationales Anmeldedatum *(Tag/Monat/Jahr)*	Prioritätsdatum *(Tag/Monat/Tag)*
PCT/DE99/02478	06/08/1999	06/08/1998
Internationale Patentklassification (IPK) oder nationale Klassifikation und IPK A61K31/00		
Anmelder VASCULAR BIOTECH GMBH et al.		

1. Dieser internationale vorläufige Prüfungsbericht wurde von der mit der internationale vorläufigen Prüfung beauftragte Behörde erstellt und wird dem Anmelder gemäß Artikel 36 übermittelt.

2. Dieser BERICHT umfaßt insgesamt 6 Blätter einschließlich dieses Deckblatts.

   ☐ Außerdem liegen dem Bericht ANLAGEN bei; dabei handelt es sich um Blätter mit Beschreibungen, Ansprüchen und/oder Zeichnungen, die geändert wurden und diesem Bericht zugrunde liegen, und/oder Blätter mit vor dieser Behörde vorgenommenen Berichtigungen (siehe Regel 70.16 und Abschnitt 607 der Verwaltungsrichtlinien zum PCT).

   Diese Anlagen umfassen insgesamt Blätter.

3. Dieser Bericht enthält Angaben zu folgenden Punkten:

   - I ☒ Grundlage des Berichts
   - II ☐ Priorität
   - III ☒ Keine Erstellung eines Gutachtens über Neuheit, erfinderische Tätigkeit und gewerbliche Anwendbarkeit
   - IV ☐ Mangelnde Einheitlichkeit der Erfindung
   - V ☒ Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderische Tätigkeit und der gewerbliche Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung
   - VI ☐ Bestimmte angeführte Unterlagen
   - VII ☒ Bestimmte Mängel der internationalen Anmeldung
   - VIII ☐ Bestimmte Bemerkungen zur internationalen Anmeldung

Datum der Einreichung des Antrags	Datum der Fertigstellung dieses Berichts
24/02/2000	16.10.2000
Name und Postanschrift der mit der internationalen vorläufigen Prüfung beauftragten Behörde: Europäisches Patentamt D-80298 München Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Bevollmächtigter Bediensteter Peris Antoli. B Tel. Nr. +49 89 2399 8476

INTERNATIONALER VORLÄUFIGER PRÜFUNGSBERICHT

Internationales Aktenzeichen PCT/DE99/02478

I. Grundlag d s B richts

1. Dieser Bericht wurde erstellt auf der Grundlage (*Ersatzblätter, die dem Anmeldeamt auf eine Aufforderung nach Artikel 14 hin vorgelegt wurden, gelten im Rahmen dieses Berichts als "ursprünglich eingereicht" und sind ihm nicht beigefügt, weil sie keine Änderungen enthalten.*):

Beschreibung, Seiten:

1-29 ursprüngliche Fassung

Patentansprüche, Nr.:

1-18 ursprüngliche Fassung

Zeichnungen, Blätter:

1/4-4/4 ursprüngliche Fassung

2. Aufgrund der Änderungen sind folgende Unterlagen fortgefallen:

☐ Beschreibung, Seiten:
☐ Ansprüche, Nr.:
☐ Zeichnungen, Blatt:

3. ☐ Dieser Bericht ist ohne Berücksichtigung (von einigen) der Änderungen erstellt worden, da diese aus den angegebenen Gründen nach Auffassung der Behörde über den Offenbarungsgehalt in der ursprünglich eingereichten Fassung hinausgehen (Regel 70.2(c)):

4. Etwaige zusätzliche Bemerkungen:

III. Keine Erstellung eines Gutachtens über Neuheit, erfinderische Tätigkeit und gewerbliche Anwendbarkeit

Folgende Teile der Anmeldung wurden nicht daraufhin geprüft, ob die beanspruchte Erfindung als neu, auf erfinderischer Tätigkeit beruhend (nicht offensichtlich) und gewerblich anwendbar anzusehen ist:

☐ die gesamte internationale Anmeldung.

☒ Ansprüche Nr. 1-2,4-12,15,16,18 (alle teilweise); 18 (gewerbliche Anwendbarkeit).

Begründung:

☒ Die gesamte internationale Anmeldung, bzw. die obengenannten Ansprüche Nr. 18 (gewerbliche Anwendbarkeit) beziehen sich auf den nachstehenden Gegenstand, für den keine internationale vorläufige Prüfung durchgeführt werden braucht (*genaue Angaben*):

siehe Beiblatt

☒ Die Beschreibung, die Ansprüche oder die Zeichnungen (*machen Sie hierzu nachstehend genaue Angaben*) oder die obengenannten Ansprüche Nr. 1-2,4-12,15,16,18 (alle teilweise) sind so unklar, daß kein sinnvolles Gutachten erstellt werden konnte (*genaue Angaben*):

siehe Beiblatt

☐ Die Ansprüche bzw. die obengenannten Ansprüche Nr. sind so unzureichend durch die Beschreibung gestützt, daß kein sinnvolles Gutachten erstellt werden konnte.

☐ Für die obengenannten Ansprüche Nr. wurde kein internationaler Recherchenbericht erstellt.

V. Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung

1. Feststellung

Neuheit (N)	Ja:	Ansprüche	1-18
	Nein:	Ansprüche	
Erfinderische Tätigkeit (ET)	Ja:	Ansprüche	1-18
	Nein:	Ansprüche	
Gewerbliche Anwendbarkeit (GA)	Ja:	Ansprüche	1-17; 18 (siehe Beiblatt)
	Nein:	Ansprüche	

2. Unterlagen und Erklärungen

siehe Beiblatt

VII. Bestimmte Mängel der internationalen Anmeldung

Es wurde festgestellt, daß die internationale Anmeldung nach Form oder Inhalt folgende Mängel aufweist:

siehe Beiblatt

Zu Punkt III

Keine Erstellung eines Gutachtens über Neuheit, erfinderische Tätigkeit und gewerbliche Anwendbarkeit

1. Der Anspruch 18 bezieht sich auf einen Gegenstand, der nach Auffassung dieser Behörde unter die Regel 67.1 (iv) PCT fällt. Daher wird über die gewerbliche Anwendbarkeit des Gegenstands dieser Ansprüche kein Gutachten erstellt (Artikel 34(4) a) (i) PCT).

2. Anspruch 1 entspricht nicht den Erfordernissen des Artikels 6 PCT, weil die technischen Angaben der Beschreibung keineswegs die Annahme stützen, daß die Kombination von

   (i) ein Hemmer der Cyclooxygenase 1 mit

   (ii) jedem beliebigen Hemmstoff der Kontraktilität venolärer Endothelzellen,

   zur gezielten Protektion des venolären Endothels und damit zur Prophylaxe und Therapie von ischemischen Organschäden und Reperfusionsyndromen führen könnte.

2.1 Wie in der Beschreibung angegeben (siehe Seite 5, Zeilen 7-11, sowie Seite 10, Zeile 24 bis Seite 11, Zeile 5) und durch die experimentellen Beispiele der Anmeldung gestützt, wird die o.g. erzielte Protektion des venolären Endothels mit einer Kombination erlangt, welche folgende Komponente enthält:

   (i) mindestens einen Hemmstoff der - durch aktivierte Leukozyten und Thrombozyten induzierbaren - Kontraktilität venolärer Endothelzellen; wie Benzopyron-Verbindungen, die spezifische Hemmwirkungen auf die Kontraktilität venolärer Endothelzellen entfalten und durch ihre antioxidanten Eigenschaften die aus aktivierten Leukozyten freigesetzten Oxidanten neutralisieren; und

   (ii) mindestens einen Hemmstoff der Cyclooxygenase 1, vorzugsweise ein nichtsteroidales Antiphlogistikum.

3. Aufgrund des vorgenannten Einwands kann für den Anspruch 1, sowie für die auf ihn bezogene Ansprüche 2, 4-12, 15, 16 und 18 kein vollständiges Gutachten erstellt werden.

3.1 Für die Erstellung dieses Berichtes ist Anspruch 1 so gelesen worden als ob er auf den Gegenstand des vorliegenden Anspruchs 3 beschränkt wäre. Die Ansprüche 2, 4-12, 15, 16 und 18 sind entsprechend interpretiert worden.

Zu Punkt V

Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung

4. Es wird auf das folgende Dokument verwiesen:

D1 = WO-A-96 35453

5. Die Ansprüche 1-18 (gelesen wie im Punkt 3.1 oben) erfüllen die Erfordernisse des Art. 33(2) und 33(3) PCT, weil ihr Gegenstand neu und erfinderisch ist (siehe unten).

5.1 **Neuheit**:

D1 ist das einzige im Recherchenbericht zitierte Dokument. Ein Wirkstoffgemisch, umfassend:

(i) mindestens eine Benzopyron-Verbindung, ausgenommen eine blutgerinnungshemmende Benzopyron-Verbindung; und

(ii) mindestens einen Hemmstoff der Cyclooxygenase 1,

wird in D1 nicht offenbart.

5.2 **Erfinderische Tätigkeit**:

Aufgabe der vorliegenden Anmeldung war es, ein Mittel zur Prophylaxe und Therapie von ischämischen Organschäden und Reperfusionssyndromen zur Verfügung zu stellen, das aber auch zur Prophylaxe und Therapie von Mikrozirkulationsstörungen aller Art (z.B. im Rahmen von arteriosklerotischen Prozessen) und der Eklampsie geeignet ist.

D1, das als nächstliegender Stand der Technik angesehen wird, offenbart (siehe z.B. Ansprüche 35-36 in Verbindung mit Seite 15, Zeilen 29-39) eine medizinische Zusammensetzung zur Behandlung von atherosklerotische vaskuläre

Krankheiten. Diese Zusammensetzung kann neben ein Endothelin Antagonist und/oder ein Hemmstoff der Endothelin-Synthase auch ein Hemmstoff der Cyclooxygenase (z.B. Aspirin oder Indometacin) enthalten.

Obwohl bekannt ist, daß Endothelin Antagonisten bzw. Hemmstoffen der Endothelin-Synthase die Kontraktilität von Endothelzellen (einschließlich Endothelzellen venolärer Ursprungs) hemmen, nichts in D1 lehrt noch legt es nahe, daß ein Wirkstoffgemisch, enthaltend

(i) mindestens eine Benzopyron-Verbindung, ausgenommen eine blutgerinnungshemmende Benzopyron-Verbindung; und

(ii) mindestens einen Hemmstoff der Cyclooxygenase 1

die gestellte Aufgabe lösen würde.

6. Die Ansprüche 1-17 erfüllen das in Art. 33(4) PCT genannte Kriterium, weil ihr Gegenstand gewerblich anwendbar ist.

7. Für die Beurteilung der Frage, ob der Gegenstand des vorliegenden Anspruchs 18 gewerblich anwendbar ist, gibt es in den PCT-Vertragsstaaten keine einheitlichen Kriterien. Die Patentierbarkeit kann auch von der Formulierung der Ansprüche abhängen. Das EPA beispielsweise erkennt den Gegenstand von Ansprüchen, die auf die medizinische Anwendung einer Verbindung gerichtet sind, nicht als gewerblich anwendbar an; es können jedoch Ansprüche zugelassen werden, die auf eine bekannte Verbindung zur erstmaligen medizinischen Anwendung und die Verwendung einer solchen Verbindung zur Herstellung eines Arzneimittels für eine neue medizinische Anwendung gerichtet sind.

Zu Punkt VII

Bestimmte Mängel der internationalen Anmeldung

8. Es ist offensichtlich, daß Anspruch 5 und Anspruch 14 sich auf Anspruch 4 (nicht 3) bzw. Anspruch 13 (nicht 12) beziehen sollten.